

FORM-PTO-1390 (Rev. 12-29-99)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER
<b>TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371</b>		<b>016800-425</b>		
INTERNATIONAL APPLICATION NO. PCT/FR99/01389		INTERNATIONAL FILING DATE 11 June 1999	U.S. APPLICATION NO. (If known, see 37 CFR 1.5) 09/719,219	
TITLE OF INVENTION <b>DIARYSELENIDE COMPOUNDS AND THEIR USE IN HUMAN OR VETERINARY MEDICINE AND IN COSMETICS</b>		PRIORITY DATE CLAIMED 12 June 1998		
APPLICANT(S) FOR DO/EO/US Jean-Michel BERNARDON; Philippe DIAZ				
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:				
<p>1. <input type="checkbox"/> This is a <b>FIRST</b> submission of items concerning a filing under 35 U.S.C. 371.</p> <p>2. <input checked="" type="checkbox"/> This is a <b>SECOND</b> or <b>SUBSEQUENT</b> submission of items concerning a filing under 35 U.S.C. 371.</p> <p>3. <input type="checkbox"/> This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and the PCT Articles 22 and 39(1).</p> <p>4. <input type="checkbox"/> A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.</p> <p>5. <input type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2))           <ul style="list-style-type: none"> <li>a. <input type="checkbox"/> is transmitted herewith (required only if not transmitted by the International Bureau).</li> <li>b. <input type="checkbox"/> has been transmitted by the International Bureau.</li> <li>c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US)</li> </ul> </p> <p>6. <input type="checkbox"/> A translation of the International Application into English (35 U.S.C. 371(c)(2)).</p> <p>7. <input type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))           <ul style="list-style-type: none"> <li>a. <input type="checkbox"/> are transmitted herewith (required only if not transmitted by the International Bureau).</li> <li>b. <input type="checkbox"/> have been transmitted by the International Bureau.</li> <li>c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired.</li> <li>d. <input type="checkbox"/> have not been made and will not be made.</li> </ul> </p> <p>8. <input type="checkbox"/> A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).</p> <p>9. <input checked="" type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).</p> <p>10. <input type="checkbox"/> A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).</p>				
Items 11. to 16. below concern other document(s) or information included:				
<p>11. <input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.</p> <p>12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.</p> <p>13. <input type="checkbox"/> A <b>FIRST</b> preliminary amendment.</p> <p><input type="checkbox"/> A <b>SECOND</b> or <b>SUBSEQUENT</b> preliminary amendment.</p> <p>14. <input type="checkbox"/> A substitute specification.</p> <p>15. <input type="checkbox"/> A change of power of attorney and/or address letter.</p> <p>16. <input checked="" type="checkbox"/> Other items or information:</p>				
PETITION FOR EXTENSION OF TIME				

FORM-PTO-1390  
(Rev. 12-29-99)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

016800-425

U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5)

99/719219

Unassigned

**TRANSMITTAL LETTER TO THE UNITED STATES  
DESIGNATED/ELECTED OFFICE (DO/EO/US)  
CONCERNING A FILING UNDER 35 U.S.C. 371**

INTERNATIONAL APPLICATION NO.  
PCT/FR99/01389INTERNATIONAL FILING DATE  
11 June 1999PRIORITY DATE CLAIMED  
12 June 1998

## TITLE OF INVENTION

DIARYSELENIDE COMPOUNDS AND THEIR USE IN HUMAN OR VETERINARY MEDICINE AND IN COSMETICS

## APPLICANT(S) FOR DO/EO/US

Jean-Michel BERNARDON, and Philippe DIAZ

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

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2.  This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3.  This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and the PCT Articles 22 and 39(1).
4.  A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
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  - a.  is transmitted herewith (required only if not transmitted by the International Bureau).
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6.  A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7.  Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
  - a.  are transmitted herewith (required only if not transmitted by the International Bureau).
  - b.  have been transmitted by the International Bureau.
  - c.  have not been made; however, the time limit for making such amendments has NOT expired.
  - d.  have not been made and will not be made.
8.  A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9.  An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10.  A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

## Items 11. to 16. below concern other document(s) or information included:

11.  An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12.  An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13.  A **FIRST** preliminary amendment.
  - A **SECOND** or **SUBSEQUENT** preliminary amendment.
14.  A substitute specification.
15.  A change of power of attorney and/or address letter.
16.  Other items or information:

U.S. APPLICATION NO. (If known, / see 37 C.F.R. § 1.56)  
Unassigned

09719219

INTERNATIONAL APPLICATION NO.  
PCT/FR99/01389ATTORNEY'S DOCKET NUMBER  
016800-425

17. <input checked="" type="checkbox"/> The following fees are submitted:		CALCULATIONS	PTO USE ONLY
<b>Basic National Fee (37 CFR 1.492(a)(1)-(5)):</b>			
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO ..... \$1,000.00 (960)			
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO ..... \$860.00 (970)			
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... \$710.00 (958)			
International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) ..... \$690.00 (956)			
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) ..... \$100.00 (962)			
<b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b>		<b>\$ 860.00</b>	
Surcharge of <b>\$130.00 (154)</b> for furnishing the oath or declaration later than months from the earliest claimed priority date (37 CFR 1.492(e)).		20 <input type="checkbox"/> 30 <input type="checkbox"/>	\$
Claims	Number Filed	Number Extra	Rate
Total Claims	19 -20 =	0	X\$18.00 (966)
Independent Claims	1 -3 =	0	X\$80.00 (964)
Multiple dependent claim(s) (if applicable)		+\$270.00 (968)	
<b>TOTAL OF ABOVE CALCULATIONS =</b>		<b>\$ 860.00</b>	
Reduction for 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).		\$	
<b>SUBTOTAL =</b>		<b>\$ 860.00</b>	
Processing fee of <b>\$130.00 (156)</b> for furnishing the English translation later than months from the earliest claimed priority date (37 CFR 1.492(f)).		20 <input type="checkbox"/> 30 <input type="checkbox"/>	\$
+			
<b>TOTAL NATIONAL FEE =</b>		<b>\$ 860.00</b>	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 (581) per property +		\$	
<b>TOTAL FEES ENCLOSED =</b>		<b>\$ 860.00</b>	
		Amount to be: refunded	\$
		charged	\$
a. <input checked="" type="checkbox"/> A check in the amount of \$ <u>860.00</u> to cover the above fees is enclosed. b. <input type="checkbox"/> Please charge my Deposit Account No. <u>02-4800</u> in the amount of \$ _____ to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. <u>02-4800</u> . A duplicate copy of this sheet is enclosed.			
<b>NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.</b>			
SEND ALL CORRESPONDENCE TO:			
Norman H. Stepno BURNS, DOANE, SWECKER & MATHIS, L.L.P. P.O. Box 1404 Alexandria, Virginia 22313-1404 (703) 836-6620			
_____ SIGNATURE			
Teresa Stanek Rea NAME			
30,427 REGISTRATION NUMBER			

09/719219  
528 Rec'd PCT/PTO 11 DEC 2000

Patent  
Attorney's Docket No. 016800-425

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of )  
Jean-Michel BERNARDON et al. ) Group Art Unit: Unassigned  
Application No.: Unassigned ) Examiner: Unassigned  
(Corresponds to PCT/FR99/01389) )  
International Filing Date: 11 June 1999 )  
For: DIARYSELENIDE COMPOUNDS )  
AND THEIR USE IN HUMAN OR )  
VETERINARY MEDICINE AND IN )  
COSMETICS )

**PRELIMINARY AMENDMENT**

**BOX PCT**

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

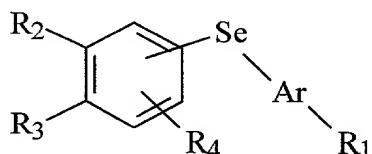
Prior to examination, please amend the above-captioned application as follows:

**IN THE CLAIMS:**

Kindly cancel claim 14 without prejudice or disclaimer.

Kindly amend the claims as follows:

1. (Amended) Compounds[, characterized in that they correspond to] having  
the general formula (I) below:



(I)

in which:

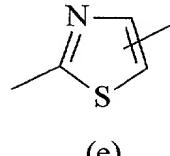
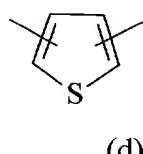
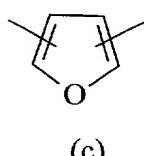
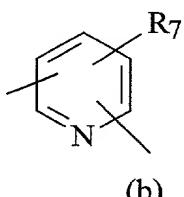
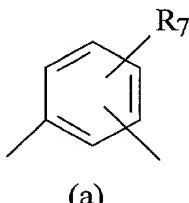
-  $R_1$  represents:

- (i) a  $-CH_3$  radical,
- (ii) a radical  $-CH_2-O-R_5$ ,
- (iii) a radical  $-COR_6$ ,

$R_5$  and  $R_6$  having the meanings given below,

-  $Ar$  represents a radical [chosen] selected from the group of radicals of formulae (a) -

(e) below:



$R_7$  having the meaning given below

-  $R_2$  and  $R_3$ , which may be identical or different, independently represent a radical

[chosen] selected from the group consisting of:

- (i) a hydrogen atom,
- (ii) a radical [chosen] selected from tert-butyl, 1-methylcyclohexyl and 1-adamantyl radicals,
- (iii) a radical  $-OR_8$ ,  $R_8$  having the meaning given below, and

(iv) a polyether radical, it being understood that at least one of the radicals  $R_2$  or  $R_3$  represents a radical (ii),

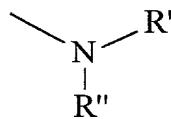
- $R_2$  and  $R_3$  taken together can form, with the adjacent aromatic ring, a 5- or 6-membered saturated ring optionally substituted with methyl groups and/or optionally interrupted with an oxygen or sulphur atom,
- $R_4$  represents a hydrogen atom, a halogen atom, a lower alkyl radical, a radical  $OR_9$ , a polyether radical or a radical  $COR_{10}$ ,

$R_9$  and  $R_{10}$  having the meanings given below,

- $R_5$  represents a hydrogen atom, a lower alkyl radical or a radical  $COR_{11}$ ,
- $R_{11}$  having the meaning given below,
- $R_6$  represents a radical [chosen] selected from the group consisting of:
  - (i) a hydrogen atom,
  - (ii) a lower alkyl radical,
  - (iii) a radical  $OR_{12}$ ,

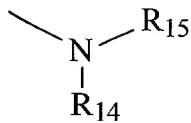
$R_{12}$  having the meaning given below, and

(iv) a radical of formula



$R'$  and  $R''$  having the meanings given below,

- $R_7$  represents a hydrogen atom, a halogen atom, a lower alkyl radical, a nitro radical, a radical  $OR_{13}$ , a polyether radical or a radical of the following formula:



R<sub>13</sub>, R<sub>14</sub> and R<sub>15</sub> having the meanings given below,

- R<sub>8</sub> represents a hydrogen atom, a lower alkyl radical, an optionally substituted aryl radical, an optionally substituted aralkyl radical, a monohydroxyalkyl or polyhydroxyalkyl radical or a lower acyl radical,
- R<sub>9</sub> represents a hydrogen atom, a lower alkyl radical, an optionally substituted aryl radical, an optionally substituted aralkyl radical, a monohydroxyalkyl or polyhydroxyalkyl radical, a lower acyl radical, a radical -(CH<sub>2</sub>)<sub>n</sub>-COOR<sub>16</sub> or a radical -(CH<sub>2</sub>)<sub>n</sub>-X,  
n, R<sub>16</sub> and X having the meanings given below,
- R<sub>10</sub> and R<sub>11</sub>, which may be identical or different, represent a lower alkyl radical,
- R<sub>12</sub> represents a hydrogen atom, a lower alkyl radical, an optionally substituted aryl or aralkyl radical, a monohydroxyalkyl radical or a polyhydroxyalkyl radical,
- R' and R'', which may be identical or different, represent a hydrogen atom, a lower alkyl radical, an optionally substituted aryl radical or an amino acid residue, or alternatively R' and R'' taken together can form, with the nitrogen atom, a heterocycle,
- R<sub>13</sub> represents a hydrogen atom or a lower alkyl radical,
- R<sub>14</sub> and R<sub>15</sub>, which may be identical or different, represent a hydrogen atom or a lower alkyl radical,
- R<sub>16</sub> represents a hydrogen atom or a lower alkyl radical,
- n represents an integer between 1 and 12 inclusive,

X represents a halogen atom, and the optical and geometrical isomers of the said compounds of formula (I), as well as the salts thereof.

2. (Amended) Compounds according to Claim 1, [characterized in that they] which are in the form of salts of an alkali metal or alkaline-earth metal, of zinc, of an organic amine or of an inorganic or organic acid.

3. (Amended) Compounds according to [either of Claims 1 and 2] claim 1, [characterized in that] wherein the lower alkyl radicals are [chosen] selected from the group consisting of methyl, ethyl, isopropyl, butyl and tert-butyl radicals.

4. (Amended) Compounds according to [one of the preceding claims] claim 1, [characterized in that] wherein the monohydroxyalkyl radicals correspond to radicals containing 2 or 3 carbon atoms, [in particular a 2-hydroxyethyl, 2-hydroxypropyl or 3-hydroxypropyl radical,] it being possible for the monohydroxyalkyl radical to be protected in the form of acetyl or tertbutyldimethylsilyl.

5. (Amended) Compounds according to [one of the preceding claims] claim 1, [characterized in that] wherein the polyhydroxyalkyl radicals are [chosen] selected from the group consisting of 2,3-dihydroxypropyl, 2,3,4-trihydroxybutyl and 2,3,4,5-

tetrahydroxypentyl radicals or a pentaerythritol residue, it being possible for the hydroxyl groups to be protected in the form of acetyls or tert-butyldimethylsilyls.

6. (Amended) Compounds according to [one of the preceding claims] claim 1, [characterized in that] wherein the aryl radicals correspond to a phenyl radical, optionally substituted with at least one halogen, one hydroxyl or one nitro function.

7. (Amended) Compounds according to [one of the preceding claims] claim 1, [characterized in that] wherein the aralkyl radicals are [chosen] selected from the group consisting of benzyl and phenethyl radicals optionally substituted with at least one halogen, one hydroxyl or one nitro function.

8. (Amended) Compounds according to [one of the preceding claims] claim 1, [characterized in that] wherein the lower acyl radicals are [chosen] selected from the group consisting of an acetyl radical [or] and a propionyl radical.

9. (Amended) Compounds according to [any one of the preceding claims] claim 1, [characterized in that] wherein the polyether radicals are [chosen] selected from the group consisting of methoxymethyl ether, methoxyethoxymethyl ether and methylthiomethyl ether radicals.

10. (Amended) Compounds according to [any one of the preceding claims]  
claim 1, [characterized in that] wherein the amino acid residues are [chosen] selected from  
the group consisting of residues derived from lysine, glycine [or from] and aspartic acid.

11. (Amended) Compounds according to [any one of the preceding claims]  
claim 1, [characterized in that] wherein the heterocyclic radicals are [chosen] selected from  
the group consisting of piperidino, morpholino, pyrrolidino and piperazino radicals,  
optionally substituted in position 4 with a C<sub>1</sub>-C<sub>6</sub> alkyl radical or with a mono- or  
polyhydroxyalkyl radical.

12. (Amended) Compounds according to Claim 1, [characterized in that they]  
which are taken, alone or as mixtures, from the group consisting of:  
ethyl 4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)benzoate, 4-  
(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)benzoic acid, ethyl 6-  
(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinate, 6-(3,5,5,8,8-  
pentamethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinic acid, ethyl 6-(5,5,8,8-  
tetramethyl-3-propoxy-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinate, 6-(5,5,8,8-  
tetramethyl-3-propoxy-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinic acid, 3-(4-tert-  
butylphenylselanyl)benzoic acid, 6-(4-tert-butylphenylselanyl)nicotinic acid, 4-(4-tert-  
butylphenylselanyl)benzoic acid, 4-(4,4-dimethylthiochroman-8-ylselanyl)benzoic acid, 3-  
(4,4-dimethylthiochroman-8-ylselanyl)benzoic acid, 6-(4,4-dimethylthiochroman-8-

ylselanyl)nicotinic acid, 4-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)benzoic acid, 3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)benzoic acid, 6-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinic acid, 4-[5-adamantan-1-yl-4-(2-methoxyethoxymethoxy)-2-methylphenylselanyl]benzoic acid, 3-[5-adamantan-1-yl-4-(2-methoxyethoxymethoxy)-2-methylphenylselanyl]benzoic acid, 6-(4-methoxyethoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinic acid, 3-(4-methoxyethoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)benzoic acid, 4-(4-methoxyethoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)-3-methoxybenzoic acid, 3-(4-methoxyethoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)-4-methoxybenzoic acid, 6-(4-methoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinic acid, 6-(3-methoxyethoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinic acid, 2-(3-methoxyethoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinic acid, 4-(3-methoxyethoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)benzoic acid, 3-(3-methoxyethoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)benzoic acid, 6-(3,5-di-tert-butyl-2-methoxymethoxyphenylselanyl)-nicotinic acid, 2-(3,5-di-tert-butyl-2-methoxymethoxyphenylselanyl)nicotinic acid, 4-(3,5-di-tert-butyl-2-methoxymethoxyphenylselanyl)benzoic acid, 3-(3,5-di-tert-butyl-2-methoxymethoxyphenylselanyl)benzoic acid, 6-[4-adamantan-1-yl-3-benzyloxyphenylselanyl)nicotinic acid, 6-(3,5-di-tert-butyl-2-



2-naphthylselanyl]benzoic acid, ethyl 4-[3-(7-methoxycarbonylheptyloxy)-5,5,8,8-tetra-methyl-5,6,7,8-tetrahydro-2-naphthylselanyl]benzoate, 4-[3-(7-carboxyheptyloxy)-5,5,8,8-tetramethyl-5,6,7,6-tetrahydro-2-naphthylselanylbenzoic acid, ethyl 6-[3-(7-methoxycarbonylheptyloxy)-5,5,8,8-tetra-methyl-5,6,7,8-tetrahydro-2-naphthylselanyl]nicotinate, 6-[3-(7-carboxyheptyloxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl]nicotinic acid, ethyl 6-[3-(2-acetoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl]nicotinate, 6-[3-(2-hydroxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl]nicotinic acid, ethyl 4-[3-(2-acetoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl]benzoate, 4-[3-(2-hydroxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl]benzoic acid, 6-(3-adamantan-1-yl-4-methoxyphenylselanyl)nicotinic acid, [6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)-3-pyridylmethanol, N-ethyl-6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinamide, morpholin-4-yl-[6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)-3-pyridyl]methanone, N-(4-hydroxyphenyl)-6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinamide, 6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)pyridine-3-carbaldehyde.

13. (Amended) Compounds according to Claim 1, [characterized in that they]  
which have at least one, [and preferably all,] of the following characteristics:

- $R_1$  represents a radical  $COR_6$
- $Ar$  represents a radical of formula (a) or (b)

- R<sub>2</sub> or R<sub>3</sub> represents an adamantyl radical or R<sub>2</sub> and R<sub>3</sub> taken together form, with the adjacent aromatic ring, a 5- or 6-membered saturated ring optionally substituted with methyl groups and/or optionally interrupted with an oxygen or sulphur atom.

15. (Amended) [Compounds according to Claim 14, for use as medicinal products intended] A method for treating dermatological complaints associated with a keratinization disorder which has a bearing on differentiation and on proliferation[, in particular for treating common acne, comedones, polymorphonuclear leukocytes, rosacea, nodulocystic acne, acne conglobata, senile acne, secondary acnes such as solar, medication-related or occupational acne]; for treating other types of keratinization disorder[, in particular ichthyosis, ichthyosiform states, Darier's disease, palmoplantar keratoderma, leucoplasias and leucoplasiform states, and cutaneous or mucous (buccal) lichen]; for treating other dermatological complaints associated with a keratinization disorder with an inflammatory and/or immunoallergic component [and, in particular, all forms of psoriasis, whether it is cutaneous, mucous or ungual psoriasis and even psoriatic rheumatism, or alternatively cutaneous atopy, such as eczema or respiratory atopy or alternatively gingival hypertrophy]; [the compounds can also be used in certain] for treating inflammatory complaints which have no keratinization disorder; for treating all dermal or epidermal proliferations, whether benign or malignant and whether they are of viral origin or otherwise[, such as common warts, flat warts and verruciform epidermodysplasia, oral or florid papillomas and proliferations which may be induced by ultraviolet radiation, in particular in the case of basocellular and spinocellular epithelioma]; for treating other

dermatological disorders such as bullous and collagen diseases; for treating certain ophthalmological disorders[, in particular corneopathies]; for repairing or combating ageing of the skin, whether this is lightinduced or chronological ageing, or for reducing actinic keratoses and pigmentations, or any pathologies associated with chronological or actinic ageing; for preventing or curing the stigmata of epidermal and/or dermal atrophy induced by local or systemic corticosteroids, or any other form of cutaneous atrophy; for preventing or treating cicatrization disorders or for preventing or repairing stretchmarks, or [alternatively] for promoting cicatrization; for combating disorders of sebaceous functioning [such as the hyperseborrhoea of acne or simple seborrhoea]; [in the treatment or prevention of] for treating or preventing cancerous or precancerous states[, more particularly promyelocyte leukaemias]; [in] for the treatment of inflammatory complaints [such as arthritis]; [in] for the treatment of any general or skin complaint of viral origin; [in] for the prevention or treatment of alopecia; [in] for the treatment of dermatological complaints having an immunological component; [in] for the treatment of complaints of the cardiovascular system [such as arteriosclerosis, hypertension, non-insulin-dependent diabetes and obesity]; [in] for the treatment of skin disorders due to an exposure to U.V. radiation comprising administering to a subject an effective amount of the compound according to claim 1 to a subject.

16. (Amended) Pharmaceutical composition[, characterized in that it comprises] comprising, in a pharmaceutically acceptable support, at least one of the compounds as defined in [any one of Claims 1 to 13] claim 1.

17. (Amended) Composition according to Claim 16, [characterized in that] wherein the concentration of compound(s) according to [one of Claims 1 to 13] claim 1 is between 0.001% and 5% by weight relative to the composition as a whole.

18. (Amended) Cosmetic composition[, characterized in that it comprises] comprising, in a cosmetically acceptable support, at least one of the compounds as defined in [any one of Claims 1 to 13] claim 1.

19. (Amended) Composition according to Claim 18, [characterized in that] wherein the concentration of compounds [according to one of Claims 1 to 13] is between 0.001% and 3% by weight relative to the composition as a whole.

20. (Amended) [Use of a cosmetic composition as defined in either of Claims 18 and 19,] A method for body or hair hygiene comprising administering an effective amount of the cosmetic composition according to claim 18 to a subject.

#### REMARKS

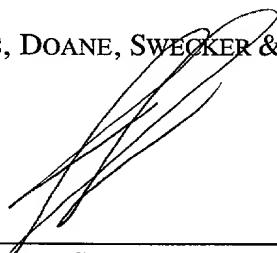
Entry of the foregoing amendment(s) is respectfully requested.

The claims have been amended to eliminate multiple dependency and to place them in better condition for U.S. patent practice.

Should the Examiner have any questions concerning the subject application, a telephone call to the undersigned would be appreciated.

Respectfully submitted,

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WO 99/65872

PCT/FR99/01389

**DIARYLSELENIDE COMPOUNDS AND USE THEREOF IN HUMAN OR  
VETERINARY MEDICINE AND IN COSMETICS**

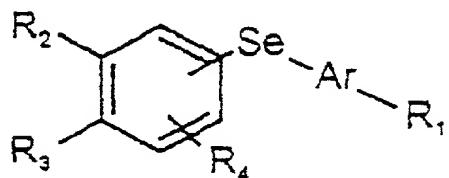
The invention relates, as novel and useful industrial products, to diarylselenide compounds. The 5 invention also relates to the use of these novel compounds in pharmaceutical compositions intended for use in human or veterinary medicine, or alternatively in cosmetic compositions.

The compounds according to the invention have 10 pronounced activity in the fields of cell proliferation and differentiation and find applications more particularly in the topical and systemic treatment of dermatological complaints associated with a keratinization disorder, dermatological (or other) 15 complaints with an inflammatory and/or immunoallergic component, and dermal or epidermal proliferations, whether benign or malignant. These compounds can also be used in the treatment of degenerative diseases of connective tissue, to combat ageing of the skin, 20 whether light-induced or chronological, and to treat cicatrization disorders. They moreover find an application in the ophthalmological field, in particular in the treatment of corneopathies.

The compounds according to the invention can 25 also be used in cosmetic compositions for body and hair hygiene.

The present invention relates to compounds

which can be represented by the general formula (I) below:



1

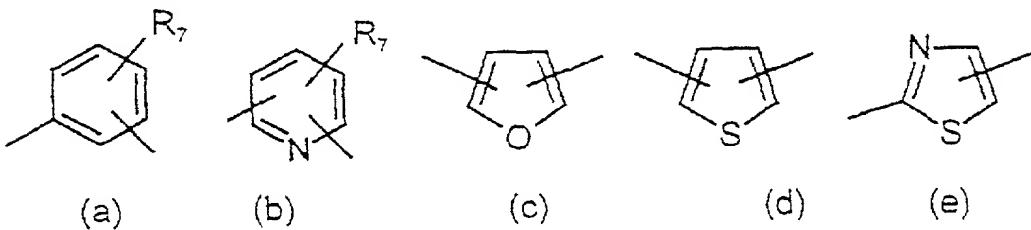
in which:

5 -  $R_1$  represents:

- (i) a  $-\text{CH}_3$  radical,
- (ii) a radical  $-\text{CH}_2-\text{O}-\text{R}_5$ ,
- (iii) a radical  $-\text{COR}_6$ ,

$R_5$  and  $R_6$  having the meanings given below,

10 - Ar represents a radical chosen from the radicals of formulae (a)-(e) below:



$R_7$  having the meaning given below.

-  $R_2$  and  $R_3$ , which may be identical or different,

15 independently represent a radical chosen from:

- (i) a hydrogen atom,
- (ii) a radical chosen from tert-butyl, 1-methylcyclohexyl and 1-adamantyl radicals,
- (iii) a radical  $-OR_8$ ,  $R_8$  having the meaning given below,
- (iv) a polyether radical,

it being understood that at least one of the radicals  $R_2$  or  $R_3$  represents a radical (ii),

-  $R_2$  and  $R_3$  taken together can form, with the adjacent aromatic ring, a 5- or 6-membered saturated ring

5 optionally substituted with methyl groups and/or optionally interrupted with an oxygen or sulphur atom,

-  $R_4$  represents a hydrogen atom, a halogen atom, a lower alkyl radical, a radical  $OR_9$ , a polyether radical or a radical  $COR_{10}$ ,

10  $R_9$  and  $R_{10}$  having the meanings given below,

-  $R_5$  represents a hydrogen atom, a lower alkyl radical or a radical  $COR_{11}$ ,

$R_{11}$  having the meaning given below,

-  $R_6$  represents a radical chosen from:

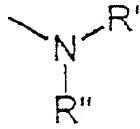
15 (i) a hydrogen atom,

(ii) a lower alkyl radical,

(iii) a radical  $OR_{12}$ ,

$R_{12}$  having the meaning given below,

(iv) a radical of formula

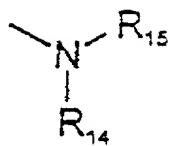


20

$R'$  and  $R''$  having the meanings given below,

-  $R_7$  represents a hydrogen atom, a halogen atom, a lower alkyl radical, a nitro radical, a radical  $OR_{13}$ , a polyether radical or a radical of the following

25 formula:



R<sub>13</sub>, R<sub>14</sub> and R<sub>15</sub> having the meanings given below,

- R<sub>8</sub> represents a hydrogen atom, a lower alkyl radical,  
5 an optionally substituted aryl radical, an optionally substituted aralkyl radical, a monohydroxyalkyl or polyhydroxyalkyl radical or a lower acyl radical,
- R<sub>9</sub> represents a hydrogen atom, a lower alkyl radical, an optionally substituted aryl radical, an optionally substituted aralkyl radical, a monohydroxyalkyl or polyhydroxyalkyl radical, a lower acyl radical, a radical -(CH<sub>2</sub>)<sub>n</sub>-COOR<sub>16</sub> or a radical -(CH<sub>2</sub>)<sub>n</sub>-X,  
10

n, R<sub>16</sub> and X having the meanings given below,

- R<sub>10</sub> and R<sub>11</sub>, which may be identical or different,  
15 represent a lower alkyl radical,
- R<sub>12</sub> represents a hydrogen atom, a lower alkyl radical, an optionally substituted aryl or aralkyl radical, a monohydroxyalkyl radical or a polyhydroxyalkyl radical,
- R' and R'', which may be identical or different,  
20 represent a hydrogen atom, a lower alkyl radical, an optionally substituted aryl radical or an amino acid residue,

or alternatively R' and R'' taken together can form, with the nitrogen atom, a heterocycle,

- 25 - R<sub>13</sub> represents a hydrogen atom or a lower alkyl radical,

- $R_{14}$  and  $R_{15}$ , which may be identical or different, represent a hydrogen atom or a lower alkyl radical,
- $R_{16}$  represents a hydrogen atom or a lower alkyl radical,

5 -  $n$  represents an integer between 1 and 12 inclusive,

- $X$  represents a halogen atom.

The invention is also directed towards the salts of the compounds of formula (I) when  $R_1$  represents a carboxylic acid function, and the geometrical and 10 optical isomers of the said compounds of formula (I).

When the compounds according to the invention are in the form of salts, they are preferably salts of an alkali metal or alkaline-earth metal, or alternatively of zinc or of an organic amine.

15 According to the present invention, the expression "lower alkyl radical" means a radical containing from 1 to 6 carbon atoms, and preferably methyl, ethyl, isopropyl, butyl and tert-butyl radicals.

20 The expression "monohydroxyalkyl radical" means a radical containing from 1 to 6 carbon atoms, in particular a 2-hydroxyethyl, 2-hydroxypropyl or 3-hydroxypropyl radical, it being possible for the monohydroxyalkyl radical to be protected in the form of 25 acetyl or tert-butyldimethylsilyl.

The expression "polyhydroxyalkyl radical" means a radical containing from 2 to 6 carbon atoms and from 2 to 5 hydroxyl groups, such as, in particular,

2,3-dihydroxypropyl, 2,3,4-trihydroxybutyl, 2,3,4,5-tetrahydroxypentyl radicals or a pentaerythritol residue, it being possible for the hydroxyl groups to be protected in the form of acetyls  
5 or tert-butyldimethylsilyls.

The expression "optionally substituted aryl radical" means a phenyl radical optionally substituted with at least one halogen atom, a hydroxyl optionally protected in the form of an ether or acetate function, 10 a nitro function or an amino function optionally substituted with an alkyl or acetyl group.

The expression "optionally substituted aralkyl radical" means a benzyl radical or a phenethyl radical optionally substituted with at least one 15 halogen atom, a hydroxyl radical optionally protected in the form of an ether or acetate function, a nitro function or an amino function optionally substituted with an alkyl or acetyl group.

The expression "lower acyl radical" means a 20 radical containing from 1 to 4 carbon atoms, and preferably an acetyl or propionyl radical.

The expression "amino acid residue" means a residue derived, for example, from one of the 20 amino acids of L or D configuration which constitute 25 mammalian proteins.

The term "heterocycle" preferably means a piperidino, morpholino, pyrrolidino or piperazino radical, optionally substituted in position 4 with a

$C_1-C_6$  alkyl radical or with a mono- or polyhydroxyalkyl radical as defined above.

The expression "polyether radical" means a radical containing from 1 to 6 carbon atoms and from 1 to 3 oxygen or sulphur atoms, such as methoxymethyl ether, methoxyethoxymethyl ether or methylthiomethyl ether radicals.

The expression "halogen atom" preferably means a fluorine, chlorine or bromine atom.

10 According to the present invention, the compounds of formula (I) that are more particularly preferred are those for which at least one, and preferably all, of the conditions below are satisfied:

- $R_1$  represents a radical  $COR_6$
- 15 -  $Ar$  represents a radical of formula (a) or (b)
- $R_2$  or  $R_3$  represents an adamantyl radical or  $R_2$  and  $R_3$  taken together form, with the adjacent aromatic ring, a 5- or 6-membered saturated ring optionally substituted with methyl groups and/or optionally 20 interrupted with an oxygen or sulphur atom.

Among the compounds of formula (I) above falling within the context of the present invention, mention may be made in particular of the following:

ethyl 4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-25 2-naphthylselanyl)benzoate,

4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)benzoic acid,

ethyl 6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-

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2-naphthylselanyl)nicotinate,  
6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-  
2-naphthylselanyl)nicotinic acid,  
ethyl 6-(5,5,8,8-tetramethyl-3-propoxy-5,6,7,8-  
5 tetrahydro-2-naphthylselanyl)nicotinate,  
6-(5,5,8,8-tetramethyl-3-propoxy-5,6,7,8-tetrahydro-  
2-naphthylselanyl)nicotinic acid,  
3-(4-tert-butylphenylselanyl)benzoic acid,  
6-(4-tert-butylphenylselanyl)nicotinic acid,  
10 4-(4-tert-butylphenylselanyl)benzoic acid,  
4-(4,4-dimethylthiochroman-8-ylselanyl)benzoic acid,  
3-(4,4-dimethylthiochroman-8-ylselanyl)benzoic acid,  
6-(4,4-dimethylthiochroman-8-ylselanyl)nicotinic acid,  
4-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl-  
15 selanyl)benzoic acid,  
3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-  
2-naphthylselanyl)benzoic acid,  
6-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-  
2-naphthylselanyl)nicotinic acid,  
20 4-[5-adamantan-1-yl-4-(2-methoxyethoxymethoxy)-  
2-methylphenylselanyl]benzoic acid,  
3-[5-adamantan-1-yl-4-(2-methoxyethoxymethoxy)-  
2-methylphenylselanyl]benzoic acid,  
6-(4-methoxyethoxymethoxy-5,5,8,8-tetramethyl-  
25 5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinic acid,  
3-(4-methoxyethoxymethoxy-5,5,8,8-tetramethyl-  
5,6,7,8-tetrahydro-2-naphthylselanyl)benzoic acid,  
4-(4-methoxyethoxymethoxy-5,5,8,8-tetramethyl-

5,6,7,8-tetrahydro-2-naphthylselanyl)-3-methoxybenzoic acid,  
3-(4-methoxyethoxymethoxy-5,5,8,8-tetramethyl-  
5,6,7,8-tetrahydro-2-naphthylselanyl)-4-methoxybenzoic  
5 acid,  
6-(4-methoxymethoxy-5,5,8,8-tetramethyl-  
5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinic acid,  
6-(3-methoxyethoxymethoxy-5,5,8,8-tetramethyl-  
5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinic acid,  
10 2-(3-methoxyethoxymethoxy-5,5,8,8-tetramethyl-  
5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinic acid,  
4-(3-methoxyethoxymethoxy-5,5,8,8-tetramethyl-  
5,6,7,8-tetrahydro-2-naphthylselanyl)benzoic acid,  
3-(3-methoxyethoxymethoxy-5,5,8,8-tetramethyl-  
15 5,6,7,8-tetrahydro-2-naphthylselanyl)benzoic acid,  
6-(3,5-di-tert-butyl-2-methoxymethoxyphenylselanyl)-  
nicotinic acid,  
2-(3,5-di-tert-butyl-2-methoxymethoxyphenylselanyl)-  
nicotinic acid,  
20 4-(3,5-di-tert-butyl-2-methoxymethoxyphenylselanyl)-  
benzoic acid,  
3-(3,5-di-tert-butyl-2-methoxymethoxyphenylselanyl)-  
benzoic acid,  
6-[4-adamantan-1-yl-3-benzyloxyphenylselanyl]nicotinic  
25 acid,  
6-(3,5-di-tert-butyl-2-benzyloxyphenylselanyl)nicotinic  
acid,  
3-methoxy-4-(4-benzyloxy-5,6,7,8-tetrahydro-

5,5,8,8-tetramethyl-2-naphthylselanyl)benzoic acid,  
4-(4-benzyloxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-  
2-naphthylselanyl)benzoic acid,  
6-(4-benzyloxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-  
5 2-naphthylselanyl)nicotinic acid,  
3-methoxy-4-(3-benzyloxy-5,6,7,8-tetrahydro-  
5,5,8,8-tetramethyl-2-naphthylselanyl)benzoic acid,  
6-(3-benzyloxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-  
2-naphthylselanyl)nicotinic acid,  
10 4-(3-hexyloxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-  
2-naphthylselanyl)-3-methoxybenzoic acid,  
6-(3-hexyloxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-  
2-naphthylselanyl)nicotinic acid,  
4-(5-adamantan-1-yl-4-benzyloxy-2-methylphenylselanyl)-  
15 benzoic acid,  
6-[3-(5-hydroxypentyloxy)-5,5,8,8-tetramethyl-  
5,6,7,8-tetrahydro-2-naphthylselanyl]nicotinic acid,  
ethyl 4-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-  
2-naphthylselanyl)benzoate,  
20 ethyl 4-(3-methoxyethoxymethoxy-5,5,8,8-tetramethyl-  
5,6,7,8-tetrahydro-2-naphthylselanyl)benzoate,  
ethyl 4-(3-hydroxy-5,5,8,8-tetramethyl-  
5,6,7,8-tetrahydro-2-naphthylselanyl)benzoate,  
4-(3-hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-  
25 2-naphthylselanyl)benzoic acid,  
ethyl 6-(3-methoxyethoxymethoxy-5,5,8,8-tetramethyl-  
5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinate,  
ethyl 6-(3-hydroxy-5,5,8,8-tetramethyl-

5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinate,  
6-(3-hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-  
2-naphthylselanyl)nicotinic acid,  
ethyl 6-[3-(3-ethoxycarbonylpropoxy)-5,5,8,8-tetramethyl-  
5 5,6,7,8-tetrahydro-2-naphthylselanyl]nicotinate,  
6-[3-(3-carboxypropoxy)-5,5,8,8-tetramethyl-  
5,6,7,8-tetrahydro-2-naphthylselanyl]nicotinic acid,  
ethyl 4-[3-(3-ethoxycarbonylpropoxy)-5,5,8,8-tetramethyl-  
5,6,7,8-tetrahydro-2-naphthylselanyl]benzoate,  
10 4-[3-(3-carboxypropoxy)-5,5,8,8-tetramethyl-  
5,6,7,8-tetrahydro-2-naphthylselanyl]benzoic acid,  
ethyl 4-[3-(7-methoxycarbonylheptyloxy)-5,5,8,8-tetra-  
methoxy-5,6,7,8-tetrahydro-2-naphthylselanyl]benzoate,  
4-[3-(7-carboxyheptyloxy)-5,5,8,8-tetramethyl-  
15 5,6,7,8-tetrahydro-2-naphthylselanyl]benzoic acid,  
ethyl 6-[3-(7-methoxycarbonylheptyloxy)-5,5,8,8-tetra-  
methoxy-5,6,7,8-tetrahydro-2-naphthylselanyl]nicotinate,  
6-[3-(7-carboxyheptyloxy)-5,5,8,8-tetramethyl-  
5,6,7,8-tetrahydro-2-naphthylselanyl]nicotinic acid,  
20 ethyl 6-[3-(2-acetoxyethoxy)-5,5,8,8-tetramethyl-  
5,6,7,8-tetrahydro-2-naphthylselanyl]nicotinate,  
6-[3-(2-hydroxyethoxy)-5,5,8,8-tetramethyl-  
5,6,7,8-tetrahydro-2-naphthylselanyl]nicotinic acid,  
ethyl 4-[3-(2-acetoxyethoxy)-5,5,8,8-tetramethyl-  
25 5,6,7,8-tetrahydro-2-naphthylselanyl]benzoate,  
4-[3-(2-hydroxyethoxy)-5,5,8,8-tetramethyl-  
5,6,7,8-tetrahydro-2-naphthylselanyl]benzoic acid,  
6-(3-adamantan-1-yl-4-methoxyphenylselanyl)nicotinic

acid,

[6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-

2-naphthylselanyl)-3-pyridyl]methanol,

N-ethyl-6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-

5 2-naphthylselanyl)nicotinamide,

morpholin-4-yl-[6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetra-

hydro-2-naphthylselanyl)-3-pyridyl]methanone,

N-(4-hydroxyphenyl)-6-(3,5,5,8,8-pentamethyl-

5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinamide,

10 6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-

2-naphthylselanyl)pyridine-3-carbaldehyde.

Subjects of the present invention are also processes for preparing the compounds of formula (I), in particular according to the reaction scheme given in

15 Figure 1.

The derivatives of formula (I) can be obtained (Fig. 1) by a sequence of reactions comprising the action of a lithiated base such as tBuLi on the product (2) in a solvent such as THF, followed by 20 addition of selenium and the formation of the dimer by oxidation in basic medium (EtOH, NaOH). The product (3) obtained is subjected to the action of sodium borohydride in a solvent such as ethanol and then coupled with an iodoaryl in the presence of a nickel 25 catalyst.

When R<sub>1</sub> represents a COOH radical, the compounds are prepared by protecting R<sub>1</sub> with a protecting group of alkyl type. Saponification of the

ester function in the presence of a base, such as sodium hydroxide or lithium hydroxide in an alcoholic solvent or in THF, gives the corresponding acids.

When  $R_1$  represents an alcohol radical, the 5 compounds can be obtained from the acid by reduction in the presence of hydride such as boron hydride. The alcohol can be etherified according to the conventional methods.

When  $R_1$  represents an aldehyde radical, the 10 compounds can be obtained by oxidation of the corresponding alcohols by the action of manganese oxide or pyridinium dichromate.

When  $R_1$  represents an amide radical, the compounds can be obtained by converting the acid into 15 the acid chloride and then by reaction with a suitable amine.

These compounds bind to RXR receptors, some having agonist activity, others having antagonist activity.

20 The binding and transactivation properties as RXR receptor agonists can be determined by methods known in the art, such as, for example: Levin et al., Nature 1992, 355, 359-61; Allenby et al., Proc. Natl. Acad. Sci., 1993, 90, 30-4.

25 The RXR-agonist activity can also be determined by the test as described in French patent application No. 95/07301 filed on 19 June 1995 by the Applicant. This test comprises the following steps:

(i) a sufficient amount of a compound which is an active ligand of at least one receptor of the steroid/thyroid nuclear receptor superfamily, other than an RXR-receptor-specific ligand which can

5 heterodimerize with the RXRs such as an RAR-agonist molecule, is applied topically to an area of skin of a mammal, (ii) a molecule capable of presenting RXR-agonist activity is administered systemically or topically to this same area of mammalian skin before,

10 during or after step (i), and (iii) the response on the area of mammal's skin thus treated is evaluated. Thus, the response to a topical application to a mammal's ear of an RAR-agonist molecule which corresponds to an increase in the thickness of this ear can be increased

15 by administering an RXR-receptor-agonist molecule systemically or topically.

The RXR $\alpha$  -antagonist activity can be evaluated in the transactivation test by determination of the dose (IC<sub>50</sub>) which gives 50% inhibition of the

20 transactivating activity of an RXR $\alpha$ -selective agonist: 6-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)cyclopropyl]nicotinic acid (CD 3127) according to the following procedure:

HeLa cells are co-transfected with an

25 expression vector coding for RXR $\alpha$  (p565-RXR $\alpha$ ) and a reporter plasmid containing the response element 1/2 CRBP II cloned upstream of the thymidine kinase heterologous promoter and of the chloramphenicol-

acetyl-transferase (CAT) reporter gene. Eighteen hours after co-transfection, the cells are treated with a fixed concentration of CD 3127 and increasing concentrations of the molecule to be evaluated. After 5 treatment for twenty-four hours, the CAT activity is assayed by ELISA. The fixed concentration of CD3127 used is  $10^{-8}$ M and corresponds to its EC<sub>50</sub>.

A subject of the present invention is thus, as a medicinal product, the compounds of formula (I) as 10 defined above.

The compounds according to the invention are particularly suitable in the following fields of treatment:

1) for treating dermatological complaints 15 associated with a keratinization disorder which has a bearing on differentiation and on proliferation, in particular for treating common acne, comedones, polymorphonuclear leukocytes, rosacea, nodulocystic acne, acne conglobata, senile acne, secondary acnes 20 such as solar, medication-related or occupational acne,

2) for treating other types of keratinization disorder, in particular ichthyosis, ichthyosiform states, Darier's disease, palmoplantar keratoderma, leucoplasias and leucoplasiform states, and cutaneous 25 or mucous (buccal) lichen,

3) for treating other dermatological complaints associated with a keratinization disorder with an inflammatory and/or immunoallergic component and, in

particular, all forms of psoriasis, whether it is cutaneous, mucous or ungual psoriasis and even psoriatic rheumatism, or alternatively cutaneous atopy, such as eczema or respiratory atopy or alternatively 5 gingival hypertrophy; the compounds can also be used in certain inflammatory complaints which have no keratinization disorder,

4) for treating all dermal or epidermal proliferations, whether benign or malignant and whether 10 they are of viral origin or otherwise, such as common warts, flat warts and verruciform epidermodysplasia, oral or florid papillomatoses and proliferations which may be induced by ultraviolet radiation, in particular in the case of basocellular and spinocellular 15 epithelioma,

5) for treating other dermatological disorders such as bullosis and collagen diseases,

6) for treating certain ophthalmological disorders, in particular corneopathies,

20 7) for repairing or combating ageing of the skin, whether this is light-induced or chronological ageing, or for reducing actinic keratoses and pigmentations, or any pathologies associated with chronological or actinic ageing,

25 8) for preventing or curing the stigmata of epidermal and/or dermal atrophy induced by local or systemic corticosteroids, or any other form of cutaneous atrophy,

9) for preventing or treating cicatrization disorders or for preventing or repairing stretchmarks, or alternatively for promoting cicatrization,

10) for combating disorders of sebaceous 5 functioning such as the hyperseborrhoea of acne or simple seborrhoea,

11) in the treatment or prevention of cancerous or precancerous states, more particularly promyelocyte leukaemias,

10 12) in the treatment of inflammatory complaints such as arthritis,

13) in the treatment of any general or skin complaint of viral origin,

14) in the prevention or treatment of alopecia,

15 15) in the treatment of dermatological or general complaints having an immunological component,

16) in the treatment of complaints of the cardiovascular system such as arteriosclerosis, hypertension, non-insulin-dependent diabetes and 20 obesity,

17) in the treatment of skin disorders due to an exposure to U.V. radiation.

In the therapeutic fields mentioned above, the compounds according to the invention may be 25 employed advantageously in combination with other compounds of retinoid-type activity, with D vitamins or derivatives thereof, with corticosteroids, with anti-free-radical agents,  $\alpha$ -hydroxy or  $\alpha$ -keto acids or

derivatives thereof, or alternatively with ion-channel blockers. The expression "D vitamins or derivatives thereof" means, for example, vitamin D<sub>2</sub> or D<sub>3</sub> derivatives and in particular 1,25-dihydroxyvitamin D<sub>3</sub>.

5 The expression "anti-free-radical agents" means, for example,  $\alpha$ -tocopherol, superoxide dismutase, ubiquinol or certain metal-chelating agents. The expression " $\alpha$ -hydroxy or  $\alpha$ -keto acids or derivatives thereof" means, for example, lactic, malic, citric, glycolic, mandelic, tartaric, glyceric or ascorbic acid salicylic acid derivatives, or the salts, amides or esters thereof. Lastly, the term "ion-channel blockers" means, for example, Minoxidil (2,4-diamino-6-piperidinopyrimidine 3-oxide) and derivatives thereof.

10 15 A subject of the present invention is also medicinal compositions containing at least one compound of formula (I) as defined above, one of the optical or geometrical isomers thereof or one of the salts thereof.

20 A subject of the present invention is thus a novel medicinal composition intended in particular for treating the abovementioned complaints, and which is characterized in that it comprises, in a pharmaceutically acceptable support which is compatible 25 with the mode of administration selected for this composition, at least one compound of formula (I), one of the optical or geometrical isomers thereof or one of the salts thereof.

The compounds according to the invention may be administered enterally, parenterally, topically or ocularly.

Via the enteral route, the medicinal products 5 may be in the form of tablets, gelatin capsules, sugar-coated tablets, syrups, suspensions, solutions, powders, granules, emulsions, microspheres or nanospheres or polymeric or lipid vesicles which enable controlled release. Via the parenteral route, the 10 compositions may be in the form of solutions or suspensions for infusion or for injection.

The compounds according to the invention are generally administered at a daily dose of about 0.01 mg/kg to 100 mg/kg of body weight taken in 1 to 3 15 doses.

Via the topical route, the pharmaceutical compositions based on compounds according to the invention are more particularly intended for the treatment of the skin and the mucosae and may thus be 20 in the form of ointments, creams, milks, salves, powders, impregnated pads, solutions, gels, sprays, lotions or suspensions. They may also be in the form of 25 microspheres or nanospheres or polymeric or lipid vesicles or polymeric patches and hydrogels which enable controlled release. These topical-route compositions may either be in anhydrous form or in aqueous form, depending on the clinical indication.

Via the ocular route, they are mainly eyedrops.

These compositions for topical or ocular use contain at least one compound of formula (I) as defined 5 above, or one of the optical or geometrical isomers thereof or alternatively one of the salts thereof, at a concentration preferably of between 0.001% and 5% by weight relative to the total weight of the composition.

The compounds of formula (I) according to the 10 invention also find an application in the cosmetic field, in particular in body and hair hygiene and especially for treating skin types with a tendency towards acne, for promoting the regrowth of the hair, for combating hair loss, for combating the greasy 15 appearance of the skin or the hair, in protection against the harmful effects of the sun or in the treatment of physiologically dry skin types, and for preventing and/or combating light-induced or chronological ageing.

20 In the cosmetic field, the compounds according to the invention can moreover be employed advantageously in combination with other compounds of retinoid-type activity, with D vitamins or derivatives thereof, with corticosteroids, with anti-free-radical 25 agents,  $\alpha$ -hydroxy or  $\alpha$ -keto acids or derivatives thereof, or alternatively with ion-channel blockers, all of these various products being as defined above.

The present invention is thus also directed towards a cosmetic composition which is characterized in that it comprises, in a cosmetically acceptable support which is suitable for topical application, at 5 least one compound of formula (I) as defined above or one of the optical or geometrical isomers thereof or one of the salts thereof, it being possible for this cosmetic composition to be, in particular, in the form of a cream, a milk, a lotion, a gel, microspheres or 10 nanospheres or polymeric or lipid vesicles, a soap or a shampoo.

The concentration of compound of formula (I) in the cosmetic compositions according to the invention is advantageously between 0.001% and 3% by weight 15 relative to the composition as a whole.

The medicinal and cosmetic compositions according to the invention can also contain inert additives or even pharmacodynamically or cosmetically active additives or combinations of these additives 20 and, in particular: wetting agents; depigmenting agents such as hydroquinone, azelaic acid, caffeic acid or kojic acid; emollients; moisturizing agents such as glycerol, PEG 400, thiamorpholinone and derivatives thereof, or urea; anti-seborrhoea or anti-acne agents 25 such as S-carboxymethylcysteine, S-benzylcysteamine, the salts and the derivatives thereof, or benzoyl peroxide; antibiotics such as erythromycin and esters thereof, neomycin, clindamycin and esters thereof, and

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tetracyclines; antifungal agents such as ketoconazole or 4,5-polymethylene-3-isothiazolidones; agents for promoting the regrowth of the hair, such as Minoxidil (2,4-diamino-6-piperidinopyrimidine 3-oxide) and

5 derivatives thereof, Diazoxide (7-chloro-3-methyl-1,2,4-benzothiadiazine 1,1-dioxide) and Phenytoin (5,5-diphenylimidazolidine-2,4-dione); non-steroidal anti-inflammatory agents; carotenoids and, in particular,  $\beta$ -carotene; anti-psoriatic agents such as

10 anthraline and derivatives thereof; and, lastly, eicosa-5,8,11,14-tetraynoic acid and eicosa-5,8,11-triynoic acid, the esters and the amides thereof.

The compositions according to the invention may also contain flavour-enhancing agents, preserving agents such as para-hydroxybenzoic acid esters, stabilizing agents, moisture regulators, pH regulators, osmotic pressure modifiers, emulsifying agents, UV-A and UV-B screening agents, and antioxidants such as  $\alpha$ -tocopherol, butylhydroxyanisole or

20 butylhydroxytoluene.

Several examples for obtaining active compounds of formula (I) according to the invention, as well as various concrete formulations based on such compounds, will now be given for illustrative purposes

25 and with no limiting nature.

A. EXAMPLES OF COMPOUNDS**EXAMPLE 1:****Ethyl 4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)benzoate**

5 (a) 5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethylnaphthalene-2-diselenide

1.7 M tert-butyllithium in pentane

(37.4 mmol, 22 ml) is added to a solution of 2-bromo-5,6,7,8-tetrahydro-3,5,5,8,8-pentamethylnaphthalene

10 (4.4 g, 15.8 mmol) in THF (100 ml) at -78°C over 10 min. The mixture is stirred at 0°C for 30 min.

Selenium (1.33 g, 16.8 mmol) is added in 2 portions.

The mixture is stirred at 0°C for 15 min and then at room temperature for 30 min. 1N HCl solution (40 ml) is

15 added and the reaction mixture is then treated with ethyl ether. The organic phase is washed twice with water, dried over anhydrous magnesium sulphate and concentrated on a rotary evaporator under vacuum at 40°C. 10 ml of ethanol and 50 mg of sodium hydroxide

20 are added to the oil obtained. The mixture is stirred vigorously for a few minutes in air (until the product has all precipitated) and is then concentrated on a rotary evaporator under vacuum at 40°C. The solid obtained is filtered through silica (eluting with

25 heptane) and then crystallized from an ethanol/ether mixture. Yellow solid. Mass: 3.26 g. Yield: 74%.

m.p.: 126°C.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 1.14 (6H, s), 1.23 (6H, s), 1.61 (4H,

s), 2.35 (3H, s), 7.05 (1H Ar, s), 7.55 (1H Ar, s).

(b) Ethyl 4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)benzoate

A solution of 5,6,7,8-tetrahydro-3,5,5,8,8-

5 pentamethylnaphthalene-2-diselenide (500 g, 0.89 mmol) and sodium borohydride (68 mg, 1.8 mmol) in 5 ml of ethanol is stirred for 1 hour at room temperature.

Ethyl iodobenzoate (440 mg, 1.6 mmol) and bis(bipyridine)nickel(II) bromide (10 mg, 0.016 mmol) 10 (Organometallics 1985, 4, 657-661) are then added. The solution is refluxed for 5 minutes. At room temperature, it is diluted with ethyl ether. The organic phase is washed with water, dried over anhydrous magnesium sulphate and then concentrated. The 15 residue is purified by fast plug (eluent: heptane and then ethyl ether).

White solid. Mass: 495 mg. Yield: 72%. m.p.: 104°C.  
1H NMR (CDCl<sub>3</sub>): 1.22 (6H, s), 1.29 (6H, s), 1.33-1.39 (3H, t), 1.67 (4H, s), 2.32 (3H, s), 4.29-4.38 (2H, q), 20 7.21-7.26 (3H, c), 7.51 (1H, s), 7.84-7.87 (2H, d).

**EXAMPLE 2:**

**4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)benzoic acid**

Sodium hydroxide (450 mg, 11.25 mmol) is 25 added to a solution of ethyl 4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)benzoate (450 mg, 1.04 mmol) in a mixture of 10 ml of THF, 1 ml of methanol and 1 ml of water. The reaction medium is

refluxed for 12 h. It is then poured into an ethyl ether/water mixture, acidified to pH 1 with concentrated hydrochloric acid solution and extracted with ethyl ether. After separation of the phases by settling, the organic phase is washed twice with water, dried over anhydrous magnesium sulphate and concentrated on a rotary evaporator under vacuum at 40°C.

White powder. Mass: 371 mg. Yield: 88%. m.p.: 249°C.  
1H NMR (CDCl<sub>3</sub>): 1.21 (6H, s), 1.29 (6H, s), 1.67 (4H, s), 2.32 (3H, s), 7.21-7.24 (2H, d, J=6.9 Hz), 7.38 (1H, s), 7.48 (1H, s), 7.85-7.88 (2H, d, J=8.35 Hz).

**EXAMPLE 3:**

**Ethyl 6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinate**

In a manner similar to that of Example 1(b), by reaction of 750 mg (1.33 mmol) of diselenide in 15 ml of ethanol with 102 mg (2.7 mmol) of sodium borohydride, 665 mg (2.4 mmol) of ethyl 6-iodonicotinate and 15 mg (0.024 mmol) of bis(bipyridine)nickel(II) bromide, 779 mg (75%) of the expected derivative are obtained in the form of a white solid. m.p.: 117°C.

1H NMR (CDCl<sub>3</sub>): 1.25 (6H, s), 1.31 (6H, s), 1.34-1.40 (3H, t), 1.69 (4H, s), 2.37 (3H, s), 4.32-4.40 (2H, q), 6.83-6.87 (1H, d, J=8.3 Hz), 7.28 (1H, s), 7.65 (1H, s), 7.91-7.96 (1H, dd, J=6.10 Hz, J'=2.21 Hz), 8.99-9.00 (1H, d, J=2.14 Hz).

**EXAMPLE 4:****6-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinic acid**

In a manner similar to that of Example 2, by reaction of 750 mg (1.74 mmol) of ethyl 6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)-nicotinate with 700 mg (17.5 mmol) of sodium hydroxide in a THF/methanol/water mixture, 625 mg (89%) of a white cottony product are obtained. m.p.: 258°C.

1H NMR (DMSO): 1.05 (6H, s), 1.11 (6H, s), 1.48 (4H, s), 2.14 (3H, s), 6.79-6.83 (1H, d,  $J=8.3$  Hz), 7.24 (1H, s), 7.45 (1H, s), 7.83-7.88 (1H, dd,  $J=6.03$  Hz,  $J'=2.3$  Hz), 8.69-8.70 (1H, d,  $J=2.2$  Hz), 13.12 (1H, s).

**EXAMPLE 5:****Ethyl 6-(5,5,8,8-tetramethyl-3-propoxy-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinate**

(a) 1,1,4,4,-Tetramethyl-7-propoxy-1,2,3,4-tetrahydronaphthalene-6-diselenide

In a manner similar to that of Example 1(a), by reaction of 6 g (18.5 mmol) of 6-bromo-1,1,4,4-tetramethyl-7-propoxy-1,2,3,4-tetrahydronaphthalene with 1.7 M tert-butyllithium in pentane and selenium in 20 ml of THF, 3.2 g of the expected selenium derivative are obtained in the form of a yellow solid.

m.p.: 92-98°C.

1H NMR ( $CDCl_3$ ): 1.05-1.10 (6H, m), 1.25 (9H, m), 1.55-1.66 (4H, m), 1.86 (2H, sext), 3.98 (2H, t), 6.67 (1H, s), 7.42 (1H, s).

(b) Ethyl 6-(5,5,8,8-tetramethyl-3-propoxy-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinate

In a manner similar to that of Example 1(b), by reaction of 850 mg (1.31 mmol) of diselenide in 85 ml of ethanol with 120 mg (2.62 mmol) of sodium borohydride, 581 mg (2.1 mmol) of ethyl 6-iodonicotinate and 20 mg (0.032 mmol) of bis(bipyridine)nickel(II) bromide, 610 mg (61%) of the expected compound are obtained in the form of white 10 crystals. m.p.: 110-112°C.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 0.81-0.87 (3H, t), 1.24 (6H, s), 1.31 (6H, s), 1.35-1.41 (3H, t), 1.57-1.65 (2H, m), 1.69 (4H, s), 3.87-3.92 (2H, t), 4.32-4.41 (2H, q), 6.66 (1H, s), 7.00-7.03 (1H, d, J=8.3 Hz), 7.59 (1H, s), 15 7.91-7.95 (1H, dd, J=6.2 Hz, J'=2.1 Hz), 8.98-8.99 (1H, d, J=1.7 Hz).

**EXAMPLE 6:**

**6-(5,5,8,8-Tetramethyl-3-propoxy-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinic acid**

In a manner similar to that of Example 2, by reaction of 485 mg (1.02 mmol) of ethyl 6-(5,5,8,8-tetramethyl-3-propoxy-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinate with 385 mg (9.6 mmol) of sodium hydroxide in ethanol (20 ml), 444 mg (97%) of a 25 white solid are obtained. m.p.: 220°C.

**EXAMPLE 7:**

**3-(4-tert-Butylphenylselenaryl)benzoic acid**

A mixture of 4-tert-butylphenyl diselenide

(0.3 mmol), 480 mg of borohydride polymer supported on Amberlyst IRA 400 resin at 2.5 mmol/g (Aldrich), bis(bipyridine)nickel(II) dibromide (5 mg) (Organometallics 1985, 4, 657-661) and ethyl 5 3-iodobenzoate (0.4 mmol) is heated for 12 h at 67°C. The mixture is filtered and the solution is concentrated. The solid obtained is purified on an SPE cartridge packed with silica gel. The fractions containing the expected product are combined and 10 concentrated under vacuum. The ester is saponified in a mixture of 2.5 ml of THF, 2.5 ml of ethyl alcohol and 0.5 ml of aqueous 33% sodium hydroxide solution. The reaction medium is acidified with HCl solution, extracted with ethyl ether, dried over magnesium sulphate and concentrated to give the expected product. 15  $^1\text{H}$  NMR/CDCl<sub>3</sub>: 1.32 (s, 9H); 7.32 to 7.38 (m, 3H); 7.46 (d, 2H); 7.61 (d, 1H); 7.95 (d, 1H); 8.19 (d, 1H).

**EXAMPLE 8:**

**6-(4-*tert*-Butylphenylselenaryl)nicotinic acid**

20 The product is obtained in a manner similar to that of Example 7, starting with 4-*tert*-butylphenyl diselenide and ethyl 6-iodonicotinate.

$^1\text{H}$  NMR/CDCl<sub>3</sub>: 1.36 (s, 9H); 7.02 (d, 1H); 7.45 (d, 2H); 7.65 (d, 2H); 7.96 (d, 1H); 9.05 (d, 1H).

25 **EXAMPLE 9:**

**4-(4-*tert*-Butylphenylselenaryl)benzoic acid**

The product is obtained in a manner similar to that of Example 7, starting with 4-*tert*-butylphenyl

diselenide and ethyl 4-iodobenzoate.

<sup>1</sup>H NMR/CDCl<sub>3</sub>: 1.34 (s, 9H); 7.35 (d, 2H); 7.39 (d, 2H); 7.54 (d, 2H); 7.92 (d, 2H).

**EXAMPLE 10**

5 **4-(4,4-Dimethylthiochroman-8-ylselenaryl)benzoic acid**

(a) 2-Bromo-1-(3-methylbut-2-enylthio)benzene

19.30 g (102.0 mmol) of 2-bromothiophenol, 160 ml of DMF and 15.50 g (112.0 mmol) of potassium carbonate are introduced into a three-necked flask.

10 13 ml (112.0 mmol) of 1-bromo-3-methyl-2-butene are added dropwise and the mixture is stirred at room temperature for two hours. The reaction medium is poured into water and extracted with ethyl acetate, and the organic phase is separated out by settling, washed 15 with water, dried over magnesium sulphate and evaporated. 26.00 g (99%) of the expected compound are collected in the form of an orange-coloured oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.65 (s, 3H), 1.73 (s, 3H), 3.56 (d, 2H, J=7.7 Hz), 5.32 (td, 1H, J=7.7/1.4 Hz), 6.96 to 20 7.06 (m, 1H), 7.22 to 7.26 (m, 2H), 7.52 (d, 1H, J=7.7 Hz).

(b) 4,4-Dimethyl-8-bromothiochroman

26.00 g (102.0 mmol) of 2-bromo-1-(3-methylbut-2-enylthio)benzene, 180 ml of toluene 25 and 23.20 g (122.0 mmol) of para-toluenesulphonic acid are introduced into a three-necked flask. The reaction medium is refluxed for four hours and evaporated to dryness. The residue is taken up in aqueous sodium

hydrogen carbonate solution and extracted with ethyl acetate, and the organic phase is separated out by settling, dried over magnesium sulphate and evaporated. The residue obtained is purified by chromatography on a 5 column of silica, eluting with heptane. 20.00 g (76%) of the expected compound are collected in the form of an orange-coloured oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.33 (s, 6H), 1.94 (t, 2H, J=6.0 Hz), 3.04 (t, 2H, J=6.1 Hz), 6.89 (t, 1H, J=7.9 Hz), 7.34 10 (d, 2H, J=7.9 Hz).

(c) 4,4-Dimethylthiochroman-8-diselenide

One crystal of iodine, magnesium (208 mg, 8.56 mmol) and a few drops of a solution of 4,4-dimethyl-8-bromothiochroman (2 g, 7.78 mmol) in 15 ethyl ether (15 ml) are heated until the organomagnesium reagent has been initiated. The rest of the solution is then added dropwise. The reaction medium is heated for 2 h and selenium (615 mg, 7.78 mmol) is then added at room temperature. Stirring 20 is continued for 30 min and 1N HCl solution is then added. The reaction mixture is treated with ethyl ether. The organic phase is washed twice with water, dried over anhydrous magnesium sulphate and concentrated on a rotary evaporator under vacuum at 25 40°C. Ethanol and sodium hydroxide are added to the oil obtained. The mixture is stirred vigorously for a few minutes and is then concentrated on a rotary evaporator under vacuum at 40°C.

The product is purified on a column of silica (20 dichloromethane/80 heptane).

White solid. Mass: 300 mg. Yield: 15%.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 1.33 (6H, s), 1.96 (2H, m), 3.09 (2H, 5 m), 6.93 (1H Ar, t, J=7.8 Hz), 7.26 (1H Ar, dd, J=7.8 Hz, J=1.3 Hz), 7.47 (1H Ar, dd, J=7.8 Hz, J=1.3 Hz).

(d) 4-(4,4-Dimethylthiochroman-8-ylselenaryl)benzoic acid

10 The product is obtained in a manner similar to that of Example 7, starting with 4,4-dimethylthiochroman-8-diselenide and ethyl 4-iodobenzoate.

<sup>1</sup>H NMR/CDCl<sub>3</sub>: 1.36 (s, 6H); 1.95 (m, 2H), 2.99 (m, 2H), 6.99 (t, 1H), 7.31 to 7.46 (m, 4H); 7.91 (d, 2H).

15 **EXAMPLE 11:**

3-(4,4-Dimethylthiochroman-8-ylselenaryl)benzoic acid

20 The product is obtained in a manner similar to that of Example 7, starting with 4,4-dimethylthiochroman-8-diselenide and ethyl 3-iodobenzoate.

<sup>1</sup>H NMR/CDCl<sub>3</sub>: 1.35 (s, 6H); 1.95 (m, 2H), 3.02 (m, 2H), 6.94 (t, 1H), 7.18 (dd, 1H); 7.33 to 7.39 (m, 2H), 7.61 (dd, 1H), 8.08 (dd, 1H), 8.16 (d, 1H).

**EXAMPLE 12:**

25 6-(4,4-Dimethylthiochroman-8-ylselenaryl)nicotinic acid

The product is obtained in a manner similar to that of Example 7, starting with 4,4-dimethylthiochroman-8-diselenide and ethyl 6-iodonicotinate.

<sup>1</sup>H NMR/CDCl<sub>3</sub>: 1.37 (s, 6H); 1.95 (m, 2H), 2.97 (m, 2H), 6.90 (d, 1H), 7.04 (t, 1H); 7.48 to 7.57 (m, 2H), 7.96 (dd, 1H), 9.03 (d, 1H).

**EXAMPLE 13:**

5 4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-  
2-naphthylselenaryl)benzoic acid

(a) 5,6,7,8-Tetrahydro-5,5,8,8-tetramethylnaphthalene-2-diselenide

A 1.7 M solution of tert-butyllithium in  
10 pentane (37.4 mmol, 22 ml) is added to a solution of  
2-bromo-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-  
naphthalene (4.22 g, 15.8 mmol) in THF (100 ml) at  
-78°C over 10 min. The mixture is stirred at 0°C for  
30 min. Selenium (1.33 g, 16.8 mmol) is added in  
15 2 portions. The mixture is stirred at 0°C for 15 min  
and then at room temperature for 30 min. 1N HCl  
solution (40 ml) is added and the reaction mixture is  
then treated with ethyl ether. The organic phase is  
washed twice with water, dried over anhydrous magnesium  
20 sulphate and concentrated on a rotary evaporator under  
vacuum at 40°C. 10 ml of ethanol and 50 mg of sodium  
hydroxide are added to the oil obtained. The mixture is  
stirred vigorously for a few minutes in air (until all  
the product has precipitated) and is then concentrated  
25 on a rotary evaporator under vacuum at 40°C. The solid  
obtained is filtered off on silica (eluting with  
heptane) and is then crystallized from an ethanol/ether  
mixture.

Orange solid. Mass: 2.9 g. Yield: 69%.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 1.21 (6H, s), 1.25 (6H, s), 1.65 (4H, s), 7.20 (1H Ar, d, J=8.25 Hz), 7.38 (1H Ar, dd, J=1.9 Hz, J=8.25 Hz), 7.51 (1H Ar, d, J=1.9 Hz).

5 (b) 4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-2-naphthylselenaryl)benzoic acid

The product is obtained in a manner similar to that of Example 7, starting with 5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-diselenide and ethyl 10 4-iodobenzoate.

<sup>1</sup>H NMR/CDCl<sub>3</sub>: 1.26 (s, 6H); 1.30 (s, 6H), 1.70 (s, 4H), 7.27 to 7.37 (m, 4H), 7.54 (d, 1H), 7.91 (d, 2H).

**EXAMPLE 14:**

3-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-

15 2-naphthylselenaryl)benzoic acid

The product is obtained in a manner similar to that of Example 7, starting with 5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-diselenide and ethyl 4-iodobenzoate.

20 <sup>1</sup>H NMR/CDCl<sub>3</sub>: 1.25 (s, 6H); 1.27 (s, 6H), 1.68 (s, 4H), 7.24 to 7.26 (m, 2H), 7.34 (t, 1H), 7.48 (s, 1H), 7.60 (dd, 1H), 7.94 (dd, 1H), 8.19 (d, 1H).

**EXAMPLE 15:**

6-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-

25 2-naphthylselenaryl)nicotinic acid

The product is obtained in a manner similar to that of Example 7, starting with 5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-diselenide and ethyl

6-iodonicotinate.

<sup>1</sup>H NMR/CDCl<sub>3</sub>: 1.29 (s, 6H); 1.32 (s, 6H), 1.72 (s, 4H), 7.03 (s, 1H), 7.36 (d, 1H), 7.45 (dd, 1H), 7.65 (d, 1H), 7.99 (dd, 1H), 9.07 (d, 1H).

5 EXAMPLE 16:

**4-[5-Adamantan-1-yl-4-(2-methoxyethoxymethoxy)-2-methylphenylselenaryl]benzoic acid**

a) 5-Adamantan-1-yl-4-(2-methoxyethoxymethoxy)-2-methylphenyl diselenide

10 A small portion of a solution of 2-(adamantan-1-yl)-4-bromo-5-methyl-1-methoxyethoxymethoxyphenyl (17 g, 41.5 mmol) in THF (160 ml) is poured onto a mixture of magnesium (1.51 g) and one crystal of iodine, with gentle heating. When 15 the reaction medium decolourizes, the rest of the solution is added so as to maintain a gentle reflux. After the end of the addition, the solution is refluxed for 1 h. After cooling to room temperature, 3.6 g of selenium are added. The reaction medium is stirred for 20 3 h at room temperature and 1N hydrochloric acid solution (105 ml) and ethyl ether are then added to the reaction medium. The organic phase is washed with water, dried over magnesium sulphate and concentrated on a rotary evaporator. Sodium hydroxide (131 mg) and 25 ethanol (27 ml) are then added. The suspension is stirred in air and at room temperature for 12 h. The product is purified by filtration on silica, eluting with dichloromethane. 12 g (71%) of a yellow solid are

obtained. m.p. = 101°C.

<sup>1</sup>H NMR/CDCl<sub>3</sub>: 1.73 (s, 6H); 2.00 (s, 9H); 2.30 (s, 3H); 3.40 (s, 3H); 3.59 (m, 2H); 3.83 (m, 2H); 5.29 (s, 2H); 6.95 (s, 1H); 7.48 (s, 1H).

5 b) 4-[5-Adamantan-1-yl-4-(2-methoxyethoxymethoxy)-2-methylphenylselenanyl]benzoic acid

The product is obtained in a manner similar to that of Example 7, starting with 5-adamantan-1-yl-4-(2-methoxyethoxymethoxy)-2-methylphenyl diselenide 10 and ethyl 4-iodobenzoate.

<sup>1</sup>H NMR/CDCl<sub>3</sub>: 1.75 (s, 6H); 2.07 (s, 9H), 2.34 (s, 3H), 3.42 (s, 3H), 3.62 (m, 2H), 3.89 (m, 2H), 5.35 (s, 2H), 7.14 (s, 1H), 7.19 (d, 2H), 7.50 (s, 1H), 7.87 (d, 2H).

EXAMPLE 17:

15 3-[5-Adamantan-1-yl-4-(2-methoxyethoxymethoxy)-2-methylphenylselenanyl]benzoic acid

The product is obtained in a manner similar to that of Example 7, starting with 5-adamantan-1-yl-4-(2-methoxyethoxymethoxy)-2-methylphenyl diselenide 20 and ethyl 3-iodobenzoate.

<sup>1</sup>H NMR/CDCl<sub>3</sub>: 1.75 (s, 6H); 2.06 (s, 9H), 2.34 (s, 3H), 3.41 (s, 3H), 3.62 (m, 2H), 3.87 (m, 2H), 5.34 (s, 2H), 7.10 (s, 1H), 7.28 (t, 1H), 7.38 (dd, 1H), 7.47 (s, 1H), 7.87 (dd, 1H), 8.02 (d, 1H).

25 EXAMPLE 18:

6-(4-Methoxyethoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselenanyl)nicotinic acid

a) 4-Methoxyethoxymethoxy-5,6,7,8-tetrahydro-5,5,8,8-

**tetramethylnaphthalene-2-diselenide**

In a manner similar to that of Example 1(a), starting with 2-bromo-5,5,8,8-tetramethyl-4-methoxyethoxymethoxy-5,6,7,8-tetrahydronaphthalene, 5 the expected compound is obtained in the form of an orange oil.

b) 6-(4-Methoxyethoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinic acid

The product is obtained in a manner similar 10 to that of Example 7, starting with 4-methoxyethoxymethoxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-diselenide and ethyl 6-iodonicotinate.

<sup>1</sup>H NMR/CDCl<sub>3</sub>: 1.27 (s, 6H); 1.42 (s, 6H), 1.67 (m, 4H), 15 3.36 (s, 3H), 3.56 (m, 2H), 3.82 (m, 2H), 5.29 (s, 2H), 7.11 (d, 1H), 7.31 (d, 1H), 7.35 (d, 1H), 8.00 (dd, 1H), 9.06 (d, 1H).

**EXAMPLE 19:**

3-(4-Methoxyethoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)benzoic acid

The product is obtained in a manner similar 20 to that of Example 7, starting with 4-methoxyethoxymethoxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-diselenide and ethyl 25 3-iodobenzoate.

<sup>1</sup>H NMR/CDCl<sub>3</sub>: 1.26 (s, 6H); 1.38 (s, 6H), 1.62 (m, 4H), 3.36 (s, 3H), 3.53 (m, 2H), 3.78 (m, 2H), 5.22 (s, 2H), 7.12 (d, 1H), 7.15 (d, 1H), 7.35 (t, 1H), 7.65 (dd,

1H), 7.96 (dd, 1H), 8.20 (d, 1H).

**EXAMPLE 20:**

**4-(4-Methoxyethoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)-3-methoxybenzoic acid**

5 The product is obtained in a manner similar to that of Example 7, starting with 4-methoxyethoxymethoxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-diselenide and ethyl 4-iodo-3-methoxybenzoate.

10  $^1\text{H}$  NMR/CDCl<sub>3</sub>: 1.26 (s, 6H); 1.42 (s, 6H), 1.66 (m, 4H), 3.35 (s, 3H), 3.54 (m, 2H), 3.81 (m, 2H), 3.98 (s, 3H), 5.27 (s, 2H), 6.94 (d, 1H), 7.25 (d, 1H), 7.30 (d, 1H), 7.48 to 7.53 (m, 2H).

**EXAMPLE 21:**

15 **3-(4-Methoxyethoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)-4-methoxybenzoic acid**

The product is obtained in a manner similar to that of Example 7, starting with

4-methoxyethoxymethoxy-5,6,7,8-tetrahydro-

20 5,5,8,8-tetramethylnaphthalene-2-diselenide and ethyl 3-iodo-4-methoxybenzoate.

$^1\text{H}$  NMR/CDCl<sub>3</sub>: 1.25 (s, 6H); 1.40 (s, 6H), 1.65 (m, 4H), 3.34 (s, 3H), 3.53 (m, 2H), 3.80 (m, 2H), 3.97 (s, 3H), 5.26 (s, 2H), 6.88 (d, 1H), 7.21 (d, 1H), 7.24 (d, 1H), 25 7.82 (d, 1H), 7.94 (dd, 1H).

**EXAMPLE 22:**

**6-(4-Methoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinic acid**

a) 4-Methoxymethoxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-diselenide

In a manner similar to that of Example 1(a), starting with 2-bromo-5,5,8,8-tetramethyl-4-methoxymethoxy-5,6,7,8-tetrahydronaphthalene, the expected compound is obtained in the form of an orange oil.

b) 6-(4-Methoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinic acid

The product is obtained in a manner similar to that of Example 7, starting with 4-methoxymethoxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-diselenide and ethyl 6-iodonicotinate.

$^1\text{H}$  NMR/CDCl<sub>3</sub>: 1.27 (s, 6H); 1.43 (s, 6H), 1.67 (m, 4H), 3.49 (s, 3H), 5.20 (s, 2H), 7.11 (d, 1H), 7.24 (d, 1H), 7.35 (d, 1H), 8.01 (dd, 1H), 9.07 (d, 1H).

20 **EXAMPLE 23:**

**6-(3-Methoxyethoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinic acid**

a) 3-Methoxyethoxymethoxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-diselenide

25 In manner similar to that of Example 1(a), starting with 2-bromo-5,5,8,8-tetramethyl-3-methoxyethoxymethoxy-5,6,7,8-tetrahydronaphthalene, the expected compound is obtained in the form of an

orange oil.

b) 6-(3-Methoxyethoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinic acid

The product is obtained in a manner similar  
5 to that of Example 7, starting with

3-methoxyethoxymethoxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-diselenide and ethyl 6-iodonicotinate.

<sup>1</sup>H NMR/CDCl<sub>3</sub>: 1.25 (s, 6H); 1.31 (s, 6H), 1.69 (s, 4H),  
10 3.36 (s, 3H), 3.51 (m, 2H), 3.74 (m, 2H), 5.22 (s, 2H),  
7.04 (d, 1H), 7.23 (s, 1H), 7.61 (s, 1H), 7.97 (dd,  
1H), 9.05 (d, 1H).

**EXAMPLE 24:**

2-(3-Methoxyethoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinic acid

The product is obtained in a manner similar  
to that of Example 7, starting with  
3-methoxyethoxymethoxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-diselenide and ethyl  
20 2-iodonicotinate.

<sup>1</sup>H NMR/CDCl<sub>3</sub>: 1.25 (s, 6H); 1.31 (s, 6H), 1.68 (s, 4H),  
3.37 (s, 3H), 3.52 (m, 2H), 3.74 (m, 2H), 5.17 (s, 2H),  
7.10 (dd, 1H), 7.22 (s, 1H), 7.54 (s, 1H), 8.29 (dd,  
1H), 8.44 (dd, 1H).

25 **EXAMPLE 25:**

4-(3-Methoxyethoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)benzoic acid

The product is obtained in a manner similar

to that of Example 7, starting with  
3-methoxyethoxymethoxy-5,6,7,8-tetrahydro-  
5,5,8,8-tetramethylnaphthalene-2-diselenide and ethyl  
4-iodobenzoate.

5  $^1\text{H}$  NMR/CDCl<sub>3</sub>: 1.19 (s, 6H), 1.29 (s, 6H), 1.63 (s, 4H),  
3.36 (s, 3H), 3.50 (m, 2H), 3.71 (m, 2H), 5.22 (s, 2H),  
7.16 (s, 1H), 7.36 (s, 1H), 7.41 (d, 2H), 7.93 (d, 2H).

**EXAMPLE 26:**

3-(3-Methoxyethoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)benzoic acid

The product is obtained in a manner similar  
to that of Example 7, starting with  
3-methoxyethoxymethoxy-5,6,7,8-tetrahydro-  
5,5,8,8-tetramethylnaphthalene-2-diselenide and ethyl  
15 3-iodobenzoate.

$^1\text{H}$  NMR/CDCl<sub>3</sub>: 1.12 (s, 6H), 1.27 (s, 6H), 1.63 (m, 4H),  
3.37 (s, 3H), 3.52 (m, 2H), 3.77 (m, 2H), 5.26 (s, 2H),  
7.12 (s, 1H), 7.13 (s, 1H), 7.38 (t, 1H), 7.69 (dd,  
1H), 7.99 (dd, 2H), 8.25 (d, 1H).

20 **EXAMPLE 27:**

6-(3,5-Di-*tert*-butyl-2-methoxymethoxyphenylselanyl)-  
nicotinic acid

a) 2-Bromo-4,6-di-*tert*-butyl-1-methoxymethoxyphenyl.

A mixture of 2-bromo-4,6-di-*tert*-butylphenol  
25 (4.4 mmol), caesium carbonate (2.95 g) and  
methoxymethyl chloride (4.8 mmol) in DMF (18 ml) is  
stirred at room temperature for 24 h. The reaction  
medium is extracted with ethyl ether. The organic phase

is washed with water, dried over magnesium sulphate and concentrated on a rotary evaporator. The product is purified by filtration on silica.

b) 4,6-Di-tert-butyl-1-methoxymethoxyphen-2-yl  
5 diselenide.

In a manner similar to that of Example 10(c), starting with 10 g of the product obtained above, 1.1 g of magnesium and 2.63 g of selenium, 7.6 g (76%) of the expected product are obtained in the form of a yellow  
10 solid.

<sup>1</sup>H NMR/CDCl<sub>3</sub>: 1.18 (s, 9H); 1.42 (s, 9H); 3.68 (s, 3H);  
5.08 (s, 2H); 7.23 (d, 1H); 7.54 (d, 1H).

c) 6-(3,5-Di-tert-butyl-2-methoxymethoxyphenyl-  
selanyl)nicotinic acid

15 The product is obtained in a manner similar to that of Example 7, starting with 4,6-di-tert-butyl-1-methoxymethoxyphen-2-yl diselenide and ethyl 6-iodonicotinate.

1H NMR/CDCl<sub>3</sub>: 1.30 (s, 9H); 1.45 (s, 9H); 3.51 (s, 3H);  
20 5.17 (s, 2H); 6.94 (d, 1H); 7.50 (d, 1H), 7.56 (d, 1H),  
7.98 (dd, 1H), 9.05 (d, 1H).

**EXAMPLE 28:**

2-(3,5-Di-tert-butyl-2-methoxymethoxyphenylselanyl)-  
nicotinic acid

25 The product is obtained in a manner similar to that of Example 7, starting with 4,6-di-tert-butyl-1-methoxymethoxyphen-2-yl diselenide and ethyl 2-iodonicotinate.

<sup>1</sup>H NMR/CDCl<sub>3</sub>: 1.30 (s, 9H); 1.46 (s, 9H); 3.51 (s, 3H); 5.16 (s, 2H); 7.12 (dd, 1H); 7.44 (s, 1H), 8.30 (dd, 1H), 8.46 (dd, 1H).

**EXAMPLE 29:**

5 **4-(3,5-Di-tert-butyl-2-methoxymethoxyphenylselanyl)-benzoic acid**

The product is obtained in a manner similar to that of Example 7, starting with 4,6-di-tert-butyl-1-methoxymethoxyphen-2-yl diselenide and ethyl

10 **4-iodobenzoate.**

<sup>1</sup>H NMR/CDCl<sub>3</sub>: 1.25 (s, 9H); 1.44 (s, 9H); 3.55 (s, 3H); 5.15 (s, 2H); 7.33 to 7.41 (m, 3H); 7.92 (d, 2H).

**EXAMPLE 30:**

15 **3-(3,5-Di-tert-butyl-2-methoxymethoxyphenylselanyl)-benzoic acid**

The product is obtained in a manner similar to that of Example 7, starting with 4,6-di-tert-butyl-1-methoxymethoxyphen-2-yl diselenide and ethyl 3-iodobenzoate.

20 <sup>1</sup>H NMR/CDCl<sub>3</sub>: 1.20 (s, 9H); 1.44 (s, 9H); 3.60 (s, 3H); 5.17 (s, 2H); 7.15 (d, 1H), 7.32 to 7.36 (m, 2H), 7.56 (dd, 1H); 7.96 (dd, 1H), 8.18 (d, 1H).

**EXAMPLE 31:**

25 **6-[4-Adamantan-1-yl-3-benzylmethoxyphenylselenalyl]-nicotinic acid**

a) 2-(Adamantan-1-yl)-5-bromo-1-(2-methoxyethoxy-methoxy)phenyl

60% sodium hydride (2.5 g) is added

portionwise to a solution of 2-(adamantan-1-yl)-5-bromo-1-phenol (20.9 g) in a mixture of THF and DMF (5/5). Stirring is continued for 30 min at room temperature after the end of the addition, and 5 methoxyethoxymethyl chloride (8.92 g) is then added. The reaction medium is stirred for 4 h at room temperature and is then treated with water and ethyl ether. The organic phase is washed with water, dried over magnesium sulphate and concentrated. After 10 filtration on silica, 17 g (64%) of the expected product are obtained in the form of a white solid. m.p. = 88°C.

b) 4-Adamantan-1-yl-3-(2-methoxyethoxymethoxy)phenyl diselenide.

15 In a manner similar to that of Example 1(a), starting with 13.04 g of 2-(adamantan-1-yl)-5-bromo-1-methoxyethoxymethoxyphenyl, 9.9 g (76%) of the expected product are obtained in the form of a yellow oil.

20  $^1\text{H}$  NMR/CDCl<sub>3</sub>: 1.55 (s, 6H); 2.05 (d, 9H); 3.38 (s, 3H); 3.57 (m, 2H); 3.82 (m, 2H); 5.27 (s, 2H), 7.11 (d, 1H); 7.22 (dd, 1H); 7.38 (d, 1H).

c) 4-Adamantan-1-yl-3-hydroxyphenyl diselenide

25 A mixture of the product obtained above (200 mg), concentrated sulphuric acid (1.4 ml), methanol (20 ml) and THF (20 ml) is stirred for 12 h at room temperature. The reaction medium is extracted with ethyl acetate. The organic phase is washed twice with

water, dried over magnesium sulphate and concentrated on a rotary evaporator under vacuum. The expected product is purified by flash chromatography to give an orange-coloured powder.

5 d) 4-Adamantan-1-yl-3-benzyloxyphenyl diselenide.

A mixture of the product obtained above (4.4 mmol), caesium carbonate (2.95 g) and benzyl chloride (1.3 ml) in DMF (18 ml) is stirred at room temperature for 24 h. The reaction medium is extracted 10 with ethyl ether. The organic phase is washed with water, dried over magnesium sulphate and concentrated on a rotary evaporator. The product is purified by filtration on silica (heptane and then dichloromethane). The expected compound is obtained in 15 the form of a yellow powder.

e) 6-[4-Adamantan-1-yl-3-benzyloxyphenylselenanyl]-nicotinic acid

The product is obtained in a manner similar to that of Example 7, starting with 4-adamantan-1-yl-20 3-benzyloxyphenyl diselenide and ethyl 6-iodonicotinate.

$^1\text{H}$  NMR/CDCl<sub>3</sub>, acetone D<sub>6</sub>: 1.74 (s, 6H); 2.06 (s, 3H); 2.17 (s, 6H); 5.12 (s, 2H); 6.97 (d, 1H), 7.26 to 7.48 (m, 8H), 7.95 (dd, 1H), 9.04 (d, 1H).

25 EXAMPLE 32:

6-(3,5-Di-tert-butyl-2-benzyloxyphenylselenanyl)nicotinic acid

a) 3,5-Di-tert-butyl-2-benzyloxyphenyl diselenide

The procedure is identical to that followed for Example 31(c) and 31(d), applied to the product of Example 27(b).

b) 6-(3,5-Di-*tert*-butyl-2-benzylxyphenylselanyl)-  
5 nicotinic acid

The product is obtained in a manner similar to that of Example 7, starting with 3,5-di-*tert*-butyl-2-benzylxyphenyl diselenide and ethyl 6-iodonicotinate.

10  $^1\text{H}$ /CDCl<sub>3</sub>, acetone D<sub>6</sub>: 1.33 (s, 9H); 1.44 (s, 9H); 5.13 (s, 2H); 7.00 (d, 1H); 7.24 to 7.32 (m, 5H), 7.51 (d, 1H), 7.60 (d, 1H), 7.98 (dd, 1H), 9.01 (d, 1H).

**EXAMPLE 33:**

3-Methoxy-4-(4-benzylxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylselanyl)benzoic acid  
15 a) 4-Hydroxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-diselenide

The product of Example 22(a), 4-methoxymethoxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-diselenide (12.4 g), is treated in a manner similar to that of Example 15(b) to give 11 g (100%) of the expected compound in the form of a yellow solid. m.p. = 200°C.

20  $^1\text{H}$  NMR/CDCl<sub>3</sub>: 1.22 (s, 6H); 1.42 (s, 6H); 1.63 (m, 4H); 5.25 (s, 1H); 6.75 (d, 1H); 7.11 (d, 1H)  
b) 4-Benzylxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-diselenide

A mixture of the product obtained above

(2.5 g, 4.4 mmol), caesium carbonate (2.95 g) and benzyl chloride (1.3 ml) in DMF (18 ml) is stirred at room temperature for 24 h. The reaction medium is extracted with ethyl ether. The organic phase is washed 5 with water, dried over magnesium sulphate and concentrated on a rotary evaporator. The product is purified by filtration on silica (heptane and then dichloromethane). 2.1 g (63%) of the expected compound are obtained in the form of a yellow powder.

10  $^1\text{H}$  NMR/CDCl<sub>3</sub>: 1.21 (s, 6H); 1.34 (s, 6H); 1.59 (m, 4H); 4.96 (s, 2H); 7.02 (d, 1H); 7.21 (d, 1H); 7.29 to 7.41 (m, 5H).

c) 3-Methoxy-4-(4-benzyloxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylselanyl)benzoic acid

15 The product is obtained in a manner similar to that of Example 7, starting with 4-benzyloxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-diselenide and ethyl 4-iodo-3-methoxybenzoate.

16  $^1\text{H}$  NMR/CDCl<sub>3</sub>: 1.27 (s, 6H), 1.43 (s, 6H), 1.66 (m, 4H), 3.98 (s, 3H), 5.04 (s, 2H), 6.88 (d, 1H), 7.01 (d, 1H), 7.29 (s, 1H), 7.33 to 7.52 (m, 7H).

**EXAMPLE 34:**

**4-(4-Benzylxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylselanyl)benzoic acid**

25 The product is obtained in a manner similar to that of Example 7, starting with 4-benzyloxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-diselenide and ethyl 4-iodobenzoate.

<sup>1</sup>H NMR/CDCl<sub>3</sub>: 1.26 (s, 6H), 1.41 (s, 6H), 1.65 (m, 4H), 5.02 (s, 2H), 6.92 (d, 1H), 7.22 (d, 1H), 7.31 to 7.41 (m, 7H), 7.90 (d, 2H).

**EXAMPLE 35:**

5 **6-(4-Benzylxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylselanyl)nicotinic acid**

The product is obtained in a manner similar to that of Example 7, starting with 4-benzylxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-diselenide and ethyl 6-iodonicotinate.

<sup>1</sup>H NMR/CDCl<sub>3</sub>: 1.28 (s, 6H), 1.43 (s, 6H), 1.67 (m, 4H), 5.07 (s, 2H), 7.00 (d, 1H), 7.04 (d, 1H), 7.32 to 7.44 (m, 6H), 7.96 (dd, 1H), 9.06 (d, 1H).

**EXAMPLE 36:**

15 **3-Methoxy-4-(3-benzylxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylselanyl)benzoic acid**

a) 3-Hydroxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-diselenide

The product of Example 23(a), 20 3-methoxyethoxymethoxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-diselenide, is treated in a manner similar to that of Example 31(c) to give the expected compound in the form of a yellow solid (100%).

b) 3-Benzylxy-5,6,7,8-tetrahydro-5,5,8,8-

25 tetramethylnaphthalene-2-diselenide

The product above is treated in a manner similar to that of Example 33(b).

c) 3-Methoxy-4-(3-benzylxy-5,6,7,8-tetrahydro-

5,5,8,8-tetramethyl-2-naphthylselanyl)benzoic acid

The product is obtained in a manner similar to that of Example 7, starting with 3-benzyloxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-diselenide and ethyl 4-iodo-3-methoxybenzoate.

<sup>1</sup>H NMR/CDCl<sub>3</sub>: 1.22 (s, 6H), 1.25 (s, 6H), 1.67 (s, 4H), 3.97 (s, 3H), 5.07 (s, 2H), 6.89 (d, 1H), 6.90 (d, 1H), 7.22 to 7.25 (m, 5H), 7.50 to 7.53 (m, 3H).

**EXAMPLE 37:**

10 6-(3-Benzyloxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylselanyl)nicotinic acid

The product is obtained in a manner similar to that of Example 7, starting with 3-benzyloxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-diselenide and ethyl 6-iodonicotinate

<sup>1</sup>H NMR/acetone D<sub>6</sub>, CDCl<sub>3</sub>: 1.25 (s, 6H), 1.27 (s, 6H), 1.68 (s, 4H), 5.08 (s, 2H), 6.94 (s, 1H), 7.04 (d, 1H), 7.31 (s, 3H), 7.62 (s, 1H), 7.94 (dd, 1H), 9.04 (d, 1H).

20 **EXAMPLE 38:**

4-(3-Hexyloxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylselanyl)-3-methoxybenzoic acid

a) 3-Hexyloxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-diselenide

25 60% sodium hydride (225 mg, 5.63 mmol) is added portionwise to a solution of 4-hydroxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-diselenide (1.2 g, 2.56 mmol) in 15 ml of THF and 15 ml of THF.

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Stirring is continued for 30 min at room temperature after the end of the addition, and iodohexane (1 ml, 6.8 mmol) is then added. The reaction medium is stirred for 4 h at room temperature and is then treated with 5 water and ethyl ether. The organic phase is washed with water, dried over magnesium sulphate and concentrated. After purification by chromatography on silica (95 heptane/5 CH<sub>2</sub>Cl<sub>2</sub>), the product is obtained in the form of a yellow oil.

10 <sup>1</sup>H NMR/CDCl<sub>3</sub>: 0.90 (m, 9H); 1.30 to 1.48 (m, 12H); 1.59 (m, 4H); 1.77 (m, 2H); 3.85 (t, 2H); 6.92 (d, 1H); 7.17 (d, 1H).

b) 4-(3-Hexyloxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylselanyl)-3-methoxybenzoic acid

15 The product is obtained in a manner similar to that of Example 7, starting with 3-hexyloxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-diselenide and ethyl 4-iodo-3-methoxybenzoate.

16 <sup>1</sup>H NMR/CDCl<sub>3</sub>: 0.89 (t, 3H), 1.27 (s, 6H), 1.30 to 1.37 (m, 4H), 1.42 (s, 6H), 1.48 (m, 2H), 1.63 (m, 4H), 1.82 (m, 2H), 3.90 (t, 2H), 3.98 (s, 3H), 6.91 (d, 1H), 6.93 (s, 1H), 7.24 (s, 1H), 7.49 to 7.55 (m, 2H).

**EXAMPLE 39:**

20 6-(3-Hexyloxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylselanyl)nicotinic acid

The product is obtained in a manner similar to that of Example 7, starting with 3-hexyloxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-diselenide

and ethyl 6-iodonicotinate.

<sup>1</sup>H NMR/CDCl<sub>3</sub>: 0.89 (t, 3H), 1.27 (s, 6H), 1.30 to 1.37 (m, 4H), 1.42 (s, 6H), 1.48 (m, 2H), 1.63 (m, 4H), 1.84 (m, 2H), 3.92 (t, 2H), 6.97 (d, 1H), 7.08 (d, 1H), 7.29 (d, 1H), 8.00 (dd, 1H), 9.08 (d, 1H).

**EXAMPLE 40:**

4-(5-Adamantan-1-yl-4-benzyloxy-2-methylphenylselenaryl)benzoic acid

a) 5-Adamantan-1-yl-4-benzyloxy-2-methylphenyl  
10 diselenide

The procedure is identical to that followed for Example 31(c) and 31(d), applied to the product of Example 16(a).

b) 4-(5-Adamantan-1-yl-4-benzyloxy-2-methylphenylselenaryl)benzoic acid

The product is obtained in a manner similar to that of Example 7, starting with 5-adamantan-1-yl-4-benzyloxy-2-methylphenyl diselenide and ethyl 4-iodobenzoate.

20 <sup>1</sup>H NMR/acetone D<sub>6</sub>, CDCl<sub>3</sub>: 1.70 (s, 6H); 2.02 (s, 3H), 2.11 (s, 6H), 2.41 (s, 3H), 5.16 (s, 2H), 6.85 (dd, 1H), 6.98 (s, 1H), 7.35 to 7.58 (m, 6H), 7.97 (dd, 2H), 9.05 (d, 1H).

**EXAMPLE 41:**

25 Ethyl 6-[3-[5-(tert-butyldimethylsilyloxy)pentyloxy-methyl]-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylselanyl]nicotinate

a) 5-(3-Bromo-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-

## 2-naphthylloxy)pentyl acetate

A solution of 3-bromo-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-ol (10 g, 0.35 mol), 5-bromopentyl acetate (8.15 g) and potassium carbonate (33.6 g) in methyl ethyl ketone (200 ml) is refluxed for 2 hours. The reaction medium is treated with water and ethyl acetate. After separation of the phases by settling, the organic phase is washed twice with water, dried over magnesium sulphate and concentrated on a rotary evaporator under vacuum at 40°C. The product is purified by flash chromatography on a column of silica. Yellow oil. Yield: 93%.

b) [5-(3-Bromo-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylloxy)pentylloxy]-tert-  
15 butyldimethylsilane

The acetate obtained above is saponified and the resulting hydroxyl group is then protected according to the following procedure: tert-butyldimethylsilyl chloride (2.64 g) is added to a mixture of 5-(3-bromo-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylloxy)pentan-1-ol (4.3 g, 11.7 mmol) and 80% sodium hydride (422 mg) in THF (20 ml).

The mixture is stirred at room temperature for 2 h. The solution is poured into a mixture of water and ethyl acetate. The organic phase is washed twice with water, dried over magnesium sulphate and concentrated on a rotary evaporator under vacuum at 40°C. The product is purified by flash chromatography

on a column of silica.

Yellow oil. Yield: 64%.

c) 3-[5-(tert-Butyldimethylsilyloxy)pentyloxy]-

5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalene-

5 2-diselenide

The expected product is obtained from the bromo derivative obtained above, in a manner similar to that of Example 1a. Yellow oil. Yield: 10%.

d) Ethyl 6-[3-[5-(tert-butyldimethylsilyloxy)-

10 pentyloxy]-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylselanyl]nicotinate.

In a manner similar to that of Example 1(b), by reaction of 257 mg (0.27 mmol) of the diselenide obtained above in 25 ml of ethanol with 119 mg of sodium borohydride, 120 mg (0.43 mmol) of ethyl 6-iodonicotinate and 4 mg of bis(bipyridine)nickel(II) dibromide, 152 mg (56%) of the expected derivative are obtained in the form of a yellow oil.

1H NMR (CDCl<sub>3</sub>): 0.00 (6H, s), 0.85 (9H, s), 1.22 (6H, s), 1.30 (6H, s), 1.33 to 1.50 (6H, m), 1.60 to 1.67 (7H, m), 3.48 (2H, t), 3.92 (2H, t), 4.35 (2H, q), 6.84 (1H, s), 6.99 (1H, d), 7.57 (1H, s), 7.91 (1H, dd), 8.97 (1H, d).

**EXAMPLE 42:**

25 6-[3-[5-(tert-Butyldimethylsilyloxy)pentyloxy]-

5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-

2-naphthylselanyl]nicotinic acid

In a manner similar to that of Example 2, by

reaction of 312 mg (0.49 mmol) of ethyl 6-[3-[5-(tert-butyldimethylsilyloxy)pentyloxy]-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylselanyl]nicotinate with 213 mg (5.3 mmol) of sodium hydroxide in a THF/ethanol 5 mixture (5 ml/5 ml), 210 mg (71%) of a yellow powder are obtained. m.p.: 161°C.

**EXAMPLE 43:**

**6-[3-(5-Hydroxypentyloxy)-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylselanyl]nicotinic acid**

10 A mixture of the product from the above example (210 mg, 0.35 mmol), a 1M solution of tetra-n-butylammonium fluoride in THF (380  $\mu$ l) in THF (5 ml) is stirred at room temperature for 3 h. 380  $\mu$ l of the tetra-n-butylammonium fluoride solution are added to 15 the reaction medium. Stirring is continued for 3.5 h and a further 380  $\mu$ l of TBAF are added and the addition is continued for a further 1 h 20 min. The reaction medium is treated with 1N HCl solution and ethyl acetate. After separation of the phases by settling, 20 the organic phase is washed with water, dried over anhydrous magnesium sulphate and concentrated. The product is purified by crystallization in a heptane/ethyl ether mixture. Mass: 194 mg, white powder. m.p. = 190-192°C.

25 **EXAMPLE 44:**

**Ethyl 4-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)benzoate**

(a) 5,6,7,8-Tetrahydro-5,5,8,8-tetramethylnaphthalene-

## 2-diselenide

A 1.7M solution of tert-butyllithium in pentane (37.4 mmol, 22 ml) is added to a solution of 2-bromo-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-5 naphthalene (4.22 g, 15.8 mmol) in THF (100 ml) at -78°C over 10 min. The mixture is stirred at 0°C for 30 min. Selenium (1.33 g, 16.8 mmol) is added in 2 portions. The mixture is stirred at 0°C for 15 min and then at room temperature for 30 min. 1N HCl 10 solution (40 ml) is added and the reaction mixture is then treated with ethyl ether. The organic phase is washed twice with water, dried over anhydrous magnesium sulphate and concentrated on a rotary evaporator under vacuum at 40°C. 10 ml of ethanol and 50 mg of sodium 15 hydroxide are added to the oil obtained. The mixture is stirred vigorously for a few minutes in air (until all the product has precipitated) and is then concentrated on a rotary evaporator under vacuum at 40°C. The solid obtained is filtered off on silica (eluting with 20 heptane) and then crystallized from an ethanol/ether mixture.

Orange solid. Mass: 2.9 g. Yield: 69%.

1H NMR (CDCl<sub>3</sub>): 1.21 (6H, s), 1.25 (6H, s), 1.65 (4H, s), 7.20 (1H Ar, d, J=8.25 Hz), 7.38 (1H Ar, dd, 25 J=1.9 Hz, J=8.25 Hz), 7.51 (1H Ar, d, J=1.9 Hz).  
b) Ethyl 4-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)benzoate

In a manner similar to that of Example 1(b),

by reaction of 213 mg (0.4 mmol) of the diselenide obtained above in 20 ml of ethanol with 73 mg of sodium borohydride (1.92 mmol), 177 mg (0.64 mmol) of ethyl 4-iodobenzoate and 37 mg of tetrakis(triphenylphosphine)palladium, and after purification by flash chromatography (70 heptane/30 CH<sub>2</sub>Cl<sub>2</sub>), 151 mg of the expected derivative are obtained in the form of a yellow solid. m.p. = 73°C.

1H NMR (CDCl<sub>3</sub>): 1.26 (6H, s), 1.29 (6H, s), 1.37 (t, 3H), 1.70 (4H, s), 4.34 (q, 2H), 7.15 to 7.25 (m, 3H), 7.32 (1H, d), 7.44 (1H, d), 7.89 (1H, d).

**EXAMPLE 45:**

**Ethyl 4-(3-methoxyethoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)benzoate**

In a manner similar to that of Example 1(b), by reaction of 3.35 g (4.5 mmol) of 3-methoxyethoxymethoxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-diselenide in 100 ml of ethanol with 501 mg of sodium borohydride (13.5 mmol), 2.5 g (9 mmol) of ethyl 4-iodobenzoate and 90 mg of bis(bipyridine)nickel(II) dibromide, and after purification by flash chromatography (85 heptane/15 EtOAc), 2.58 g of the expected derivative are obtained in the form of a yellow oil (83%).

**EXAMPLE 46:**

**Ethyl 4-(3-hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)benzoate**

A mixture of ethyl 4-(3-methoxyethoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)benzoate (2.3 g, 4.4 mmol), concentrated sulphuric acid (475  $\mu$ l), methanol (40 ml) and THF (20 ml) is stirred for 48 h at room temperature. The reaction medium is extracted with ethyl ether. The 10 organic phase is washed twice with water, dried over magnesium sulphate and concentrated on a rotary evaporator under vacuum. The product is purified by crystallization from heptane. 2.06 g (97%) of the expected compound are obtained in the form of an 15 orange-coloured powder. m.p. = 113°C.

**EXAMPLE 47:**

**4-(3-Hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)benzoic acid**

In a manner similar to that of Example 2, by 20 reaction of 400 mg (0.92 mmol) of ethyl 4-(3-hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)benzoate with 336 mg (8.4 mmol) of sodium hydroxide in a THF/ethanol mixture (20 ml/20 ml), 214 mg (58%) of a pink powder are 25 obtained. m.p. = 217°C.

**EXAMPLE 48:****Ethyl 6-(3-methoxyethoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinate**

In a manner similar to that of Example 1(b),  
 5 by reaction of 3.35 g (4.5 mmol) of  
 3-methoxyethoxymethoxy-5,6,7,8-tetrahydro-5,5,8,8-  
 tetramethylnaphthalene-2-diselenide in 100 ml of  
 ethanol with 501 mg of sodium borohydride (13.5 mmol),  
 2.5 g (9 mmol) of ethyl 4-iodobenzoate and 90 mg of  
 10 bis(bipyridine)nickel(II) dibromide, and after  
 purification by flash chromatography  
 (85 heptane/15 EtOAc), 2.09 g of the expected  
 derivative are obtained in the form of a yellow oil  
 (45%).  
 15  $^1\text{H}$  NMR/CDCl<sub>3</sub>: 1.25 (s, 6H), 1.31 (s, 6H), 1.38 (t, 3H),  
 1.69 (m, 4H), 3.36 (s, 3H), 3.50 (m, 2H), 3.73 (m, 2H),  
 4.37 (q, 2H), 5.22 (s, 2H), 7.01 (d, 1H), 7.22 (s, 1H),  
 7.60 (s, 1H), 7.94 (dd, 1H), 8.99 (d, 1H).

**EXAMPLE 49:**  
 20 **Ethyl 6-(3-hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinate**

A mixture of ethyl 6-(3-methoxyethoxymethoxy-  
 5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-  
 2-naphthylselanyl)nicotinate (2.6 g, 5 mmol),  
 25 concentrated sulphuric acid (535  $\mu\text{l}$ ), ethanol (75 ml)  
 and THF (25 ml) is stirred for 3 days at room  
 temperature. The reaction medium is extracted with  
 ethyl ether. The organic phase is washed twice with

water, dried over magnesium sulphate and concentrated on a rotary evaporator under vacuum. The solid obtained is washed with ethyl ether. 2.01 g (93%) of the expected compound are obtained in the form of an 5 orange-coloured powder. m.p. = 138°C.

**EXAMPLE 50:**

**6-(3-Hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinic acid**

In a manner similar to that of Example 2, by 10 reaction of 400 mg (0.92 mmol) of ethyl 6-(3-hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinate with 357 mg (8.9 mmol) of sodium hydroxide in a THF/ethanol mixture (20 ml/20 ml), 60 mg (16%) of a yellow powder are 15 obtained. m.p.: 250°C.

**EXAMPLE 51:**

**Ethyl 6-[3-(3-ethoxycarbonylpropoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl]-nicotinate**

20 432 mg (102.0 mmol) of ethyl 6-(3-hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinate, 276 mg (2 mmol) of potassium carbonate and 390 mg (2 mmol) of ethyl 4-bromobutanoate are introduced into a three-necked 25 flask. The mixture is heated at 80°C for 12 h. The reaction medium is poured into water and extracted with ethyl ether, and the organic phase is separated out by settling, washed with water, dried over magnesium

sulphate and evaporated. After purification by flash chromatography (9 heptane/1 EtOAc), 467 mg (85%) of the expected compound are collected in the form of an orange-coloured oil.

5     <sup>1</sup>H NMR/CDCl<sub>3</sub>: 1.20 to 1.31 (m, 15H), 1.38 (t, 3H), 1.69 (s, 4H), 1.96 (m, 2H), 2.38 (t, 2H), 2.85 (t, 2H), 4.12 (q, 2H), 4.36 (q, 2H), 6.88 (d, 1H), 7.02 (s, 1H), 7.48 (s, 1H), 8.26 (dd, 2H), 8.83 (d, 1H).

**EXAMPLE 52:**

10    **6-[3-(3-Carboxypropoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl]nicotinic acid**

In a manner similar to that of Example 2, by reaction of 340 mg (0.62 mmol) of ethyl 6-[3-(3-ethoxycarbonylpropoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl]nicotinate with 250 mg (62.2 mmol) of sodium hydroxide in ethanol (10 ml), 211 mg (69%) of a white powder are obtained.  
m.p.: 177°C.

**EXAMPLE 53:**

20    **Ethyl 4-[3-(3-ethoxycarbonylpropoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl]-benzoate**

In a manner similar to that of Example 51, by reaction of 300 mg (0.86 mmol) of ethyl 4-(3-hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)benzoate with 336 mg (1.72 mmol) of ethyl 4-bromobutanoate and 238 mg of potassium carbonate in MEK (10 ml), 364 mg (78%) of a yellow oil are obtained.

<sup>1</sup>H NMR/CDCl<sub>3</sub>: 1.16 to 1.32 (m, 15H), 1.38 (t, 3H), 1.66 (m, 4H), 1.98 (m, 2H), 2.30 (t, 2H), 3.98 (t, 2H), 4.08 (q, 2H), 4.35 (q, 2H), 6.78 (s, 1H), 7.28 (s, 1H), 7.41 (dd, 2H), 7.87 (dd, 2H).

5 **EXAMPLE 54:**

**4-[3-(3-Carboxypropoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl]benzoic acid**

In manner similar to that of Example 2, by reaction of 250 mg (0.46 mmol) of ethyl 10 4-[3-(3-carboxypropoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl]benzoate with 183 mg (4.6 mmol) of sodium hydroxide in a THF/ethanol mixture (5 ml/5 ml), 172 mg (76%) of a white powder are obtained. m.p.: 230°C.

15 **EXAMPLE 55:**

**Ethyl 4-[3-(7-methoxycarbonylheptyloxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl]-benzoate**

In a manner similar to that of Example 51, by 20 reaction of 370 mg (0.86 mmol) of ethyl 4-(3-hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)benzoate with 408 mg (1.72 mmol) of methyl 8-bromoocanoate and 238 mg of potassium carbonate in MEK (10 ml), 502 mg (99%) of a yellow oil 25 are obtained.

<sup>1</sup>H NMR/CDCl<sub>3</sub>: 1.16 (s, 6H), 1.26 to 1.29 (m, 12H), 1.38 (t, 3H), 1.56 to 1.68 (m, 8H), 2.28 (t, 2H), 3.66 (s, 3H), 3.92 (t, 2H), 4.36 (q, 2H), 6.78 (s, 1H), 7.27

(s, 1H), 7.41 (dd, 2H), 7.88 (dd, 2H).

**EXAMPLE 56:**

**4-[3-(7-Carboxyheptyloxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl]benzoic acid**

5 In a manner similar to that of Example 2, by reaction of 410 mg (0.7 mmol) of ethyl 4-[3-(7-methoxycarbonylheptyloxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl]benzoate with 280 mg (7 mmol) of sodium hydroxide in a THF/ethanol 10 mixture (5 ml/5 ml), 326 mg (85%) of a white powder are obtained. m.p.: 183°C.

**EXAMPLE 57:**

**Ethyl 6-[3-(7-methoxycarbonylheptyloxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl]-15 nicotinate**

In a manner similar to that of Example 51, by reaction of 460 mg (1.06 mmol) of ethyl 6-(3-hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinate with 515 mg (2.17 mmol) of 20 methyl 8-bromoocanoate and 295 mg of potassium carbonate in MEK (10 ml), 487 mg (78%) of a yellow oil are obtained.

**EXAMPLE 58:**

**6-[3-(7-Carboxyheptyloxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl]nicotinic [lacuna]**

In a manner similar to that of Example 2, by reaction of 390 mg (0.66 mmol) of ethyl 6-[3-(7-methoxycarbonylheptyloxy)-5,5,8,8-tetramethyl-

5,6,7,8-tetrahydro-2-naphthylselanyl]nicotinate with 265 mg (6.6 mmol) of sodium hydroxide in a THF/ethanol mixture (5 ml/1 ml), 277 mg (77%) of a white powder are obtained. m.p.: 186°C.

5 **EXAMPLE 59:**

**Ethyl 6-(3-(2-acetoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinate**

a) 2-Bromoethyl acetate

Acetic anhydride (11.35 ml, 0.12 mol) is 10 added dropwise to a solution of 2-bromoethanol (12.5 g, 0.1 mol) and DMAP (1.22 g) in 125 ml of dichloromethane. The mixture is stirred at room temperature for 12 h and treated with water and dichloromethane. The organic phase is washed with 15 water, dried over magnesium sulphate, concentrated on a rotary evaporator and purified by distillation.

Yellowish liquid (94%).

b) **Ethyl 6-(3-(2-acetoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinate**

20 In a manner similar to that of Example 51, by reaction of 477 mg (1.10 mmol) of ethyl 6-(3-hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinate with 396 mg (2.2 mmol) of 2-bromoethyl acetate and 304 mg of potassium carbonate 25 in MEK (10 ml), 545 mg (96%) of a yellow oil are obtained.

<sup>1</sup>H NMR/CDCl<sub>3</sub>: 1.24 (s, 6H), 1.32 (s, 6H), 1.38 (t, 3H), 1.69 (s, 4H), 1.99 (s, 3H), 3.00 (t, 3H), 4.24 (t, 2H),

4.38 (q, 2H), 6.89 (d, 1H), 7.03 (s, 1H), 7.54 (s, 1H),  
8.27 (dd, 1H), 8.83 (d, 1H).

**EXAMPLE 60:**

**6-(3-(2-Hydroxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-**  
**5 tetrahydro-2-naphthylselanyl)nicotinic acid**

In a manner similar to that of Example 2, by reaction of 419 mg (0.81 mmol) of ethyl 6-[3-(2-acetoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl]nicotinate with 320 mg (8 mmol) of sodium hydroxide in a THF/ethanol mixture (4 ml/4 ml), 273 mg (75%) of a white powder are obtained. m.p.: 170°C.

**EXAMPLE 61:**

**Ethyl 4-(3-(2-acetoxyethoxy)-5,5,8,8-tetramethyl-15,6,7,8-tetrahydro-2-naphthylselanyl)benzoate**

In a manner similar to that of Example 51, by reaction of 400 mg (0.93 mmol) of ethyl 4-(3-hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)benzoate with 334 mg (2.2 mmol) of 2-bromoethyl acetate and 257 mg of potassium carbonate in MEK (10 ml), 333 mg (69%) of a yellow oil are obtained.

<sup>1</sup>H NMR/CDCl<sub>3</sub>: 1.16 (s, 6H), 1.29 (s, 6H), 1.38 (t, 3H), 1.59 (s, 4H), 1.99 (s, 3H), 4.16 (m, 2H), 4.29 to 4.40 (m, 4H), 6.82 (s, 1H), 7.28 (s, 1H), 7.43 (d, 1H), 7.89 (d, 1H).

**EXAMPLE 62:****4-(3-(2-Hydroxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)benzoic acid**

In a manner similar to that of Example 2, by  
5 reaction of 322 mg (0.62 mmol) of ethyl  
4-[3-(2-acetoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl]benzoate with 250 mg  
(6.2 mmol) of sodium hydroxide in a THF/ethanol mixture  
(3 ml/3 ml), 226 mg (81%) of a white powder are  
10 obtained. m.p.: 197°C.

**EXAMPLE 63:****Ethyl 4-(3-(2-chloroethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)benzoate**

In a manner similar to that of Example 51, by  
15 reaction of 431 mg (1 mmol) of ethyl 4-(3-hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl benzoate with 222 mg (1.5 mmol) of  
1-bromo-2-chloroethyl [lacuna] and 278 mg of potassium  
carbonate in MEK (20 ml), 200 mg (40%) of a yellow oil  
20 are obtained.

**EXAMPLE 64:****Ethyl 4-[3-(2-iodoethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl]benzoate**

A mixture of 200 mg (0.4 mmol) of ethyl  
25 4-[3-(2-chloroethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthylselanyl]benzoate with 607 mg  
(4 mmol) of sodium iodide in MEK (4 ml) is refluxed for  
12 h. The reaction medium is treated with water and

ethyl ether. The organic phase is washed with water, dried over magnesium sulphate and concentrated on a rotary evaporator. The oil obtained is reacted under the same conditions. 159 mg (68%) of a yellow solid are 5 obtained. m.p. = 87°C.

**EXAMPLE 65:**

**6-(3-Adamantan-1-yl-4-methoxyphenylselanyl)nicotinic acid**

The product is obtained in a manner similar 10 to that of Example 7, starting with 3-adamantan-1-yl-4-methoxyphenyl diselenide and ethyl 6-iodonicotinate.  
<sup>1</sup>H NMR/THF D8: 1.79 (s, 6H), 2.04 (s, 3H), 2.13 (s, 6H), 3.89 (s, 3H), 6.93 (d, 1H), 7.02 (d, 1H), 7.52 to 7.55 (m, 2H), 7.91 (dd, 1H), 8.9 (d, 1H).

**EXAMPLE 66:**

**[6-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)-3-pyridyl]methanol**

3 g (7 mmol) of ethyl 6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)-20 nicotinate, 800 mg (20 mmol) of lithium aluminium hydride and 90 ml of THF are introduced into a round-bottomed flask under a stream of nitrogen. The reaction medium is refluxed for two hours, cooled, the excess hydride is hydrolysed and the salt is filtered off.  
25 After evaporation of the filtrate, the residue obtained is recrystallized from heptane. 1.36 g (50%) of [6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)-3-pyridyl]methanol with a melting

point of 110-111°C are collected.

**EXAMPLE 67:**

**N-Ethyl-6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinamide**

5 (a) 6-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinyl chloride

2 g (5 mmol) of 6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinic acid, 20 ml of toluene, 100  $\mu$ l of DMF and 450  $\mu$ l of thionyl chloride are introduced into a round-bottomed flask.

10 The reaction medium is refluxed for one hour and evaporated. 100% of the expected acid chloride are collected, this product being used for the rest of the synthesis without further purification.

15 (b) N-Ethyl-6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinamide

20 By reaction of 2.1 g (5 mmol) of the above acid chloride with 1 ml of ethylamine (70% in water) in 20 ml of THF, 2.02 g (95%) of the expected amide, with a melting point of 218-220°C, are obtained.

**EXAMPLE 68:**

**Morpholin-4-yl-[6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)-3-pyridyl]methanone**

25 By reaction of 2.1 g (5 mmol) of the above acid chloride with 1 ml of morpholine in 20 ml of THF, 2.17 g (93%) of the expected amide, with a melting point of 147-148°C, are obtained.

**EXAMPLE 69:**

**N-(4-Hydroxyphenyl)-6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinamide**

By reaction of 2.1 g (5 mmol) of the above  
 5 acid chloride with 540 mg (5 mmol) of 4-aminophenol in  
 40 ml of THF in the presence of 830  $\mu$ l of  
 triethylamine, 2.35 g (96%) of the expected amide, with  
 a melting point of 223-225°C, are obtained.

**EXAMPLE 70:**

10 **6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)pyridine-3-carbaldehyde**

By reaction of 890 mg (2.3 mmol) of  
 [6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)-3-pyridyl]methanol with 1.12 g  
 15 (3 mmol) of pyridinium dichromate in 90 ml of dichloromethane, and after filtration on silica, 600 mg (68%) of 6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylselanyl)pyridine-3-carbaldehyde, with a melting point of 150-152°C, are obtained.

20 **B. FORMULATION EXAMPLES**

1) ORAL ROUTE

(a) The following composition is prepared in the form of a 0.8 g tablet

	Compound of Example 3 .....	0.005 g
25	Pregelatinized starch .....	0.265 g
	Microcrystalline cellulose .....	0.300 g
	Lactose .....	0.200 g
	Magnesium stearate .....	0.030 g

For the treatment of acne, 1 to 3 tablets will be administered to an adult individual per day for 3 to 6 months, depending on the severity of the case treated.

5

(b) A drinkable suspension for packaging in 5 ml vials is prepared:

	Compound of Example 12 .....	0.050 g
	Glycerol .....	0.500 g
10	70% sorbitol .....	0.500 g
	Sodium saccharinate .....	0.010 g
	Methyl parahydroxybenzoate .....	0.040 g
	Flavouring .....	qs
	Purified water .....	qs 5 ml
15	For the treatment of acne, 1 vial will be administered to an adult individual per day for 3 months, depending on the severity of the case treated.	

20 (c) The following formulation for packaging in gelatin capsules is prepared:

	Compound of Example 5 .....	0.025 g
	Corn starch .....	0.060 g
	Lactose qs .....	0.300 g
25	The gelatin capsules used consist of gelatin, titanium oxide and a preserving agent.	

In the treatment of psoriasis, 1 gelatin capsule will be administered to an adult individual per day for 30 days.

2) TOPICAL ROUTE

5 (a) The following nonionic water-in-oil cream is prepared:

Compound of Example 23 ..... 0.100 g  
Mixture of emulsifying lanolin  
alcohols, waxes and refined oils,  
10 sold by the company BDF under the  
name "anhydrous Eucerin" ..... 39.900 g  
Methyl para-hydroxybenzoate ..... 0.075 g  
Propyl para-hydroxybenzoate ..... 0.075 g  
Sterile demineralized water qs .... 100.000 g  
15 This cream will be applied to psoriatic skin  
once or twice a day for 30 days.

(b) A gel is prepared by making the following formulation:

20 Compound of Example 39 ..... 0.050 g  
Base erythromycin ..... 4.000 g  
Butylhydroxytoluene ..... 0.050 g  
Hydroxypropylcellulose sold by  
the company Hercules under the  
name "Klucel HF" ..... 2.000 g  
25 Ethanol (at 95°) qs ..... 100.000 g  
This gel will be applied to skin affected  
with dermatitis or acneic skin 1 to 3 times a day for 6

to 12 weeks, depending on the severity of the case treated.

(c) An anti-seborrhoeic lotion is prepared by mixing 5 together the following ingredients:

Compound of Example 6 .....	0.030 g
Propylene glycol .....	5.000 g
Butylhydroxytoluene .....	0.100 g
Ethanol (at 95°) qs .....	100.000 g

10 This lotion will be applied twice a day to a seborrhoeic scalp, and a significant improvement is observed within a period of between 2 and 6 weeks.

(d) A cosmetic composition to combat the harmful 15 effects of the sun is prepared by mixing together the following ingredients:

Compound of Example 59 .....	1.000 g
Benzylidene camphor .....	4.000 g
Fatty acid triglycerides .....	31.000 g
20 Glyceryl monostearate .....	6.000 g
Stearic acid .....	2.000 g
Cetyl alcohol .....	1.200 g
Lanolin .....	4.000 g
Preserving agents .....	0.300 g
25 Propylene glycol .....	2.000 g
Triethanolamine .....	0.500 g
Fragrance .....	0.400 g
Demineralized water qs .....	100.000 g

This composition will be applied daily and makes it possible to combat light-induced ageing.

(e) The following nonionic oil-in-water cream is  
5 prepared:

	Compound of Example 16 .....	0.500 g
	Vitamin D3 .....	0.020 g
	Cetyl alcohol .....	4.000 g
	Glyceryl monostearate .....	2.500 g
10	PEG-50 stearate .....	2.500 g
	Karite butter .....	9.200 g
	Propylene glycol .....	2.000 g
	Methyl para-hydroxybenzoate .....	0.075 g
	Propyl para-hydroxybenzoate .....	0.075 g
15	Sterile demineralized water qs .....	100.000 g

This cream will be applied to psoriatic skin  
once or twice a day for 30 days.

(f) A topical gel is prepared by mixing together the  
20 following ingredients:

	Compound of Example 4 .....	0.050 g
	Ethanol .....	43.000 g
	$\alpha$ -tocopherol .....	0.050 g
	Carboxyvinyl polymer sold under	
25	the name "Carbopol 941" by the	
	company "Goodrich" .....	0.500 g
	Triethanolamine as an aqueous	
	solution at 20% by weight .....	3.800 g

Water ..... 9.300 g

Propylene glycol qs ..... 100.000 g

This gel will be applied in the treatment of  
acne 1 to 3 times a day for 6 to 12 weeks, depending on  
5 the severity of the case treated.

(g) A hair lotion to combat hair loss and to promote  
regrowth of the hair is prepared by mixing together the  
following ingredients:

10 Compound of Example 31 ..... 0.05 g

Compound sold under the name

"Minoxidil" ..... 1.00 g

Propylene glycol ..... 20.00 g

Ethanol ..... 34.92 g

15 Polyethylene glycol (molecular  
mass = 400) ..... 40.00 g

Butylhydroxyanisole ..... 0.01 g

Butylhydroxytoluene ..... 0.02 g

Water qs ..... 100.00 g

20 This lotion will be applied twice a day for  
3 months to a scalp which has suffered considerable  
hair loss.

(h) An anti-acne cream is prepared by mixing together  
25 the following ingredients:

Compound of Example 7 ..... 0.050 g

Retinoic acid ..... 0.010 g

Mixture of glycerol stearate and

polyethylene glycol stearate (75 mol),  
 sold under the name "Gelot 64" by  
 the company "Gattefosse" ..... 15.000 g  
 Kernel oil polyoxyethylenated with  
 5 6 mol of ethylene oxide, sold  
 under the name "Labrafil M2130 CS"  
 by the company "Gattefosse" ..... 8.000 g  
 Perhydrosqualene ..... 10.000 g  
 Preserving agents ..... qs

10 Polyethylene glycol (molecular  
 mass = 400) ..... 8.000 g  
 Disodium salt of ethylenediamine-  
 tetraacetic acid ..... 0.050 g  
 Purified water qs ..... 100.000 g

15 This cream will be applied to skin affected  
 with dermatitis or to acneic skin 1 to 3 times a day  
 for 6 to 12 weeks.

(i) An oil-in-water cream is prepared by making the  
 20 following formulation:

Compound of Example 43 ..... 0.020 g  
 Betamethasone 17-valerate ..... 0.050 g  
 S-Carboxymethylcysteine ..... 3.000 g  
 Polyoxyethylene stearate (40 mol of  
 25 ethylene oxide) sold under the name  
 "Myrj 52" by the company "Atlas" ..... 4.000 g  
 Sorbitan monolaurate, polyoxyethylene  
 with 20 mol of ethylene oxide, sold

under the name "Tween 20" by the  
company "Atlas" ..... 1.800 g

Mixture of glyceryl mono- and  
distearate sold under the name  
"Geleol" by the company "Gattefosse". 4.200 g

5 Propylene glycol ..... 10.000 g

Butylhydroxyanisole ..... 0.010 g

Butylhydroxytoluene ..... 0.020 g

Cetostearyl alcohol ..... 6.200 g

10 Preserving agents ..... qs

Perhydrosqualene ..... 18.000 g

Mixture of caprylic/capric  
triglycerides sold under the name  
"Miglyol 812" by the company "Dynamit

15 Nobel" ..... 4.000 g

Triethanolamine (99% by weight) ..... 2.500 g

Water qs ..... 100.000 g

This cream will be applied twice a day to  
skin affected with dermatitis, for 30 days.

20

(j) The following oil-in-water cream is prepared:

Lactic acid ..... 5.000 g

Compound of Example 1 ..... 0.020 g

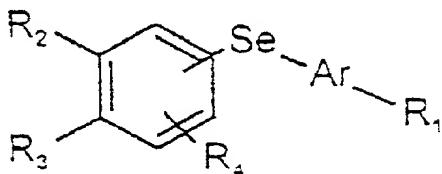
Polyoxyethylene stearate (40 mol of  
25 ethylene oxide) sold under the name  
"Myrj 52" by the company "Atlas" ..... 4.000 g

Sorbitan monolaurate, polyoxyethylene  
with 20 mol of ethylene oxide, sold

under the name "Tween 20" by the  
 company "Atlas" ..... 1.800 g  
 Mixture of glyceryl mono- and  
 distearate sold under the name  
 5 "Geleol" by the company "Gattefosse" 4.200 g  
 Propylene glycol ..... 10.000 g  
 Butylhydroxyanisole ..... 0.010 g  
 Butylhydroxytoluene ..... 0.020 g  
 Cetostearyl alcohol ..... 6.200 g  
 10 Preserving agents ..... qs  
 Perhydrosqualene ..... 18.000 g  
 Mixture of caprylic/capric  
 triglycerides sold under the name  
 "Miglyol 812" by the company "Dynamit  
 15 Nobel" ..... 4.000 g  
 Water qs ..... 100.000 g  
 This cream will be applied once a day and  
 helps to combat ageing, whether this is light-induced  
 or chronological ageing.

CLAIMS

1. Compounds, characterized in that they correspond to the general formula (I) below:

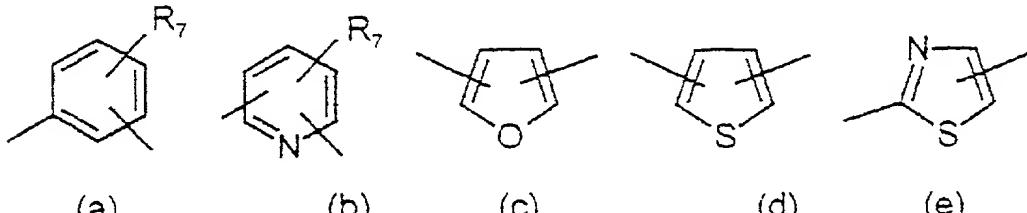


(I)

5 in which:

-  $R_1$  represents:

- (i) a  $-CH_3$  radical,
- (ii) a radical  $-CH_2-O-R_5$ ,
- (iii) a radical  $-COR_6$ ,

10  $R_5$  and  $R_6$  having the meanings given below,-  $Ar$  represents a radical chosen from the radicals of formulae (a)-(e) below:

(a)

(b)

(c)

(d)

(e)

15  $R_7$  having the meaning given below,-  $R_2$  and  $R_3$ , which may be identical or different, independently represent a radical chosen from:

- (i) a hydrogen atom,
- (ii) a radical chosen from tert-butyl, 1-methylcyclohexyl and 1-adamantyl radicals,
- (iii) a radical  $-OR_8$ ,  $R_8$  having the meaning given

below,

(iv) a polyether radical,

it being understood that at least one of the radicals  $R_2$  or  $R_3$  represents a radical (ii),

5 -  $R_2$  and  $R_3$  taken together can form, with the adjacent aromatic ring, a 5- or 6-membered saturated ring optionally substituted with methyl groups and/or optionally interrupted with an oxygen or sulphur atom,

-  $R_4$  represents a hydrogen atom, a halogen atom, a lower alkyl radical, a radical  $OR_9$ , a polyether radical or a radical  $COR_{10}$ ,

$R_9$  and  $R_{10}$  having the meanings given below,

-  $R_5$  represents a hydrogen atom, a lower alkyl radical or a radical  $COR_{11}$ ,

15  $R_{11}$  having the meaning given below,

-  $R_6$  represents a radical chosen from:

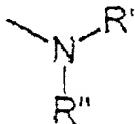
(i) a hydrogen atom,

(ii) a lower alkyl radical,

(iii) a radical  $OR_{12}$ ,

20  $R_{12}$  having the meaning given below,

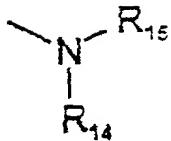
(iv) a radical of formula



$R'$  and  $R''$  having the meanings given below,

-  $R_7$  represents a hydrogen atom, a halogen atom, a lower alkyl radical, a nitro radical, a radical  $OR_{13}$ , a polyether radical or a radical of the following

formula:



$\text{R}_{13}$ ,  $\text{R}_{14}$  and  $\text{R}_{15}$  having the meanings given below,

5 -  $\text{R}_8$  represents a hydrogen atom, a lower alkyl radical, an optionally substituted aryl radical, an optionally substituted aralkyl radical, a monohydroxyalkyl or polyhydroxyalkyl radical or a lower acyl radical,

-  $\text{R}_9$  represents a hydrogen atom, a lower alkyl radical,

10 an optionally substituted aryl radical, an optionally substituted aralkyl radical, a monohydroxyalkyl or polyhydroxyalkyl radical, a lower acyl radical, a radical  $-(\text{CH}_2)_n-\text{COOR}_{16}$  or a radical  $-(\text{CH}_2)_n-\text{X}$ ,

$n$ ,  $\text{R}_{16}$  and  $\text{X}$  having the meanings given below,

15 -  $\text{R}_{10}$  and  $\text{R}_{11}$ , which may be identical or different, represent a lower alkyl radical,

-  $\text{R}_{12}$  represents a hydrogen atom, a lower alkyl radical, an optionally substituted aryl or aralkyl radical, a monohydroxyalkyl radical or a polyhydroxyalkyl radical,

20 -  $\text{R}'$  and  $\text{R}''$ , which may be identical or different, represent a hydrogen atom, a lower alkyl radical, an optionally substituted aryl radical or an amino acid residue,

or alternatively  $\text{R}'$  and  $\text{R}''$  taken together can form,

25 with the nitrogen atom, a heterocycle,

-  $\text{R}_{13}$  represents a hydrogen atom or a lower alkyl

radical,

-  $R_{14}$  and  $R_{15}$ , which may be identical or different, represent a hydrogen atom or a lower alkyl radical,

-  $R_{16}$  represents a hydrogen atom or a lower alkyl

5 radical,

-  $n$  represents an integer between 1 and 12 inclusive,

-  $X$  represents a halogen atom,

and the optical and geometrical isomers of the said compounds of formula (I), as well as the salts thereof.

10 2. Compounds according to Claim 1,

characterized in that they are in the form of salts of an alkali metal or alkaline-earth metal, of zinc, of an organic amine or of an inorganic or organic acid.

3. Compounds according to either of

15 Claims 1 and 2, characterized in that the lower alkyl radicals are chosen from methyl, ethyl, isopropyl, butyl and tert-butyl radicals.

4. Compounds according to one of the preceding claims, characterized in that the 20 monohydroxyalkyl radicals correspond to radicals containing 2 or 3 carbon atoms, in particular a 2-hydroxyethyl, 2-hydroxypropyl or 3-hydroxypropyl radical, it being possible for the monohydroxyalkyl radical to be protected in the form of acetyl or tert-25 butyldimethylsilyl.

5. Compounds according to one of the preceding claims, characterized in that the polyhydroxyalkyl radicals are chosen from

2,3-dihydroxypropyl, 2,3,4-trihydroxybutyl and 5  
2,3,4,5-tetrahydroxypentyl radicals or a  
pentaerythritol residue, it being possible for the  
hydroxyl groups to be protected in the form of acetyls  
5 or tert-butyldimethylsilyls.

6. Compounds according to one of the  
preceding claims, characterized in that the aryl  
radicals correspond to a phenyl radical, optionally  
substituted with at least one halogen, one hydroxyl or  
10 one nitro function.

7. Compounds according to one of the  
preceding claims, characterized in that the aralkyl  
radicals are chosen from benzyl and phenethyl radicals  
optionally substituted with at least one halogen, one  
15 hydroxyl or one nitro function.

8. Compounds according to one of the  
preceding claims, characterized in that the lower acyl  
radicals are chosen from an acetyl radical or a  
propionyl radical.

20 9. Compounds according to any one of the  
preceding claims, characterized in that the polyether  
radicals are chosen from methoxymethyl ether,  
methoxyethoxymethyl ether and methylthiomethyl ether  
radicals.

25 10. Compounds according to any one of the  
preceding claims, characterized in that the amino acid  
residues are chosen from the group consisting of  
residues derived from lysine, glycine or from aspartic

acid.

11. Compounds according to any one of the preceding claims, characterized in that the heterocyclic radicals are chosen from the group 5 consisting of piperidino, morpholino, pyrrolidino and piperazino radicals, optionally substituted in position 4 with a C<sub>1</sub>-C<sub>6</sub> alkyl radical or with a mono- or polyhydroxyalkyl radical.

12. Compounds according to Claim 1, 10 characterized in that they are taken, alone or as mixtures, from the group consisting of: ethyl 4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro- 15 2-naphthylselanyl)benzoate, 4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro- 2-naphthylselanyl)benzoic acid, ethyl 6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro- 20 2-naphthylselanyl)nicotinate, 6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro- 2-naphthylselanyl)nicotinic acid, ethyl 6-(5,5,8,8-tetramethyl-3-propoxy-5,6,7,8- 25 tetrahydro-2-naphthylselanyl)nicotinate, 6-(5,5,8,8-tetramethyl-3-propoxy-5,6,7,8-tetrahydro- 2-naphthylselanyl)nicotinic acid, 3-(4-tert-butylphenylselanyl)benzoic acid, 6-(4-tert-butylphenylselanyl)nicotinic acid, 4-(4-tert-butylphenylselanyl)benzoic acid, 4-(4,4-dimethylthiochroman-8-ylselanyl)benzoic acid, 3-(4,4-dimethylthiochroman-8-ylselanyl)benzoic acid,

6-(4,4-dimethylthiochroman-8-ylselanyl)nicotinic acid,  
4-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-  
2-naphthylselanyl)benzoic acid,  
3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-  
5 2-naphthylselanyl)benzoic acid,  
6-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-  
2-naphthylselanyl)nicotinic acid,  
4-[5-adamantan-1-yl-4-(2-methoxyethoxymethoxy)-  
2-methylphenylselanyl]benzoic acid,  
10 3-[5-adamantan-1-yl-4-(2-methoxyethoxymethoxy)-  
2-methylphenylselanyl]benzoic acid,  
6-(4-methoxyethoxymethoxy-5,5,8,8-tetramethyl-  
5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinic acid,  
3-(4-methoxyethoxymethoxy-5,5,8,8-tetramethyl-  
15 5,6,7,8-tetrahydro-2-naphthylselanyl)benzoic acid,  
4-(4-methoxyethoxymethoxy-5,5,8,8-tetramethyl-  
5,6,7,8-tetrahydro-2-naphthylselanyl)-3-methoxybenzoic  
acid,  
3-(4-methoxyethoxymethoxy-5,5,8,8-tetramethyl-  
20 5,6,7,8-tetrahydro-2-naphthylselanyl)-4-methoxybenzoic  
acid,  
6-(4-methoxymethoxy-5,5,8,8-tetramethyl-  
5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinic acid,  
6-(3-methoxyethoxymethoxy-5,5,8,8-tetramethyl-  
25 5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinic acid,  
2-(3-methoxyethoxymethoxy-5,5,8,8-tetramethyl-  
5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinic acid,  
4-(3-methoxyethoxymethoxy-5,5,8,8-tetramethyl-

5,6,7,8-tetrahydro-2-naphthylselanyl)benzoic acid,  
3-(3-methoxyethoxymethoxy-5,5,8,8-tetramethyl-  
5,6,7,8-tetrahydro-2-naphthylselanyl)benzoic acid,  
6-(3,5-di-tert-butyl-2-methoxymethoxyphenylselanyl)-  
5 nicotinic acid,  
2-(3,5-di-tert-butyl-2-methoxymethoxyphenylselanyl)-  
nicotinic acid,  
4-(3,5-di-tert-butyl-2-methoxymethoxyphenylselanyl)-  
benzoic acid,  
10 3-(3,5-di-tert-butyl-2-methoxymethoxyphenylselanyl)-  
benzoic acid,  
6-[4-adamantan-1-yl-3-benzyloxyphenylselanyl]nicotinic  
acid,  
6-(3,5-di-tert-butyl-2-benzyloxyphenylselanyl)nicotinic  
15 acid,  
3-methoxy-4-(4-benzyloxy-5,6,7,8-tetrahydro-  
5,5,8,8-tetramethyl-2-naphthylselanyl)benzoic acid,  
4-(4-benzyloxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-  
2-naphthylselanyl)benzoic acid,  
20 6-(4-benzyloxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-  
2-naphthylselanyl)nicotinic acid,  
3-methoxy-4-(3-benzyloxy-5,6,7,8-tetrahydro-  
5,5,8,8-tetramethyl-2-naphthylselanyl)benzoic acid,  
6-(3-benzyloxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-  
25 2-naphthylselanyl)nicotinic acid,  
4-(3-hexyloxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-  
2-naphthylselanyl)-3-methoxybenzoic acid,  
6-(3-hexyloxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-

2-naphthylselanyl)nicotinic acid,  
4-(5-adamantan-1-yl-4-benzyloxy-2-methylphenylselanyl)-  
benzoic acid,  
6-[3-(5-hydroxypentyloxy)-5,5,8,8-tetramethyl-  
5 5,6,7,8-tetrahydro-2-naphthylselanyl]nicotinic acid,  
ethyl 4-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-  
2-naphthylselanyl)benzoate,  
ethyl 4-(3-methoxyethoxymethoxy-5,5,8,8-tetramethyl-  
5,6,7,8-tetrahydro-2-naphthylselanyl)benzoate,  
10 ethyl 4-(3-hydroxy-5,5,8,8-tetramethyl-  
5,6,7,8-tetrahydro-2-naphthylselanyl)benzoate,  
4-(3-hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-  
2-naphthylselanyl)benzoic acid,  
ethyl 6-(3-methoxyethoxymethoxy-5,5,8,8-tetramethyl-  
15 5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinate,  
ethyl 6-(3-hydroxy-5,5,8,8-tetramethyl-  
5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinate,  
6-(3-hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-  
2-naphthylselanyl)nicotinic acid,  
20 ethyl 6-[3-(3-ethoxycarbonylpropoxy)-5,5,8,8-tetramethyl-  
5,6,7,8-tetrahydro-2-naphthylselanyl]nicotinate,  
6-[3-(3-carboxypropoxy)-5,5,8,8-tetramethyl-  
5,6,7,8-tetrahydro-2-naphthylselanyl]nicotinic acid,  
ethyl 4-[3-(3-ethoxycarbonylpropoxy)-5,5,8,8-tetramethyl-  
25 5,6,7,8-tetrahydro-2-naphthylselanyl]benzoate,  
4-[3-(3-carboxypropoxy)-5,5,8,8-tetramethyl-  
5,6,7,8-tetrahydro-2-naphthylselanyl]benzoic acid,  
ethyl 4-[3-(7-methoxycarbonylheptyloxy)-5,5,8,8-tetra-

methyl-5,6,7,8-tetrahydro-2-naphthylselanyl]benzoate,  
 4-[3-(7-carboxyheptyloxy)-5,5,8,8-tetramethyl-  
 5,6,7,8-tetrahydro-2-naphthylselanyl]benzoic acid,  
 ethyl 6-[3-(7-methoxycarbonylheptyloxy)-5,5,8,8-tetra-  
 5 methyl-5,6,7,8-tetrahydro-2-naphthylselanyl]nicotinate,  
 6-[3-(7-carboxyheptyloxy)-5,5,8,8-tetramethyl-  
 5,6,7,8-tetrahydro-2-naphthylselanyl]nicotinic acid,  
 ethyl 6-[3-(2-acetoxyethoxy)-5,5,8,8-tetramethyl-  
 5,6,7,8-tetrahydro-2-naphthylselanyl]nicotinate,  
 10 6-[3-(2-hydroxyethoxy)-5,5,8,8-tetramethyl-  
 5,6,7,8-tetrahydro-2-naphthylselanyl]nicotinic acid,  
 ethyl 4-[3-(2-acetoxyethoxy)-5,5,8,8-tetramethyl-  
 5,6,7,8-tetrahydro-2-naphthylselanyl]benzoate,  
 4-[3-(2-hydroxyethoxy)-5,5,8,8-tetramethyl-  
 15 5,6,7,8-tetrahydro-2-naphthylselanyl]benzoic acid,  
 6-(3-adamantan-1-yl-4-methoxyphenylselanyl)nicotinic  
 acid,  
 [6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-  
 2-naphthylselanyl)-3-pyridyl]methanol,  
 20 N-ethyl-6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-  
 2-naphthylselanyl)nicotinamide,  
 morpholin-4-yl-[6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetra-  
 hydro-2-naphthylselanyl)-3-pyridyl]methanone,  
 N-(4-hydroxyphenyl)-6-(3,5,5,8,8-pentamethyl-  
 25 5,6,7,8-tetrahydro-2-naphthylselanyl)nicotinamide,  
 6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-  
 2-naphthylselanyl)pyridine-3-carbaldehyde.

13. Compounds according to Claim 1,

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characterized in that they have at least one, and preferably all, of the following characteristics:

- $R_1$  represents a radical  $COR_6$
- $Ar$  represents a radical of formula (a) or (b)

5        -  $R_2$  or  $R_3$  represents an adamantyl radical or  $R_2$  and  $R_3$  taken together form, with the adjacent aromatic ring, a 5- or 6-membered saturated ring optionally substituted with methyl groups and/or optionally interrupted with an oxygen or sulphur atom.

10        14. Compounds according to any one of the preceding claims, for use as medicinal products.

15        15. Compounds according to Claim 14, for use as medicinal products intended for treating dermatological complaints associated with a

15        15 keratinization disorder which has a bearing on differentiation and on proliferation, in particular for treating common acne, comedones, polymorphonuclear leukocytes, rosacea, nodulocystic acne, acne conglobata, senile acne, secondary acnes such as solar, 20 medication-related or occupational acne; for treating other types of keratinization disorder, in particular ichthyosis, ichthyosiform states, Darier's disease, palmoplantar keratoderma, leucoplasias and leucoplasiform states, and cutaneous or mucous (buccal)

25        25 lichen; for treating other dermatological complaints associated with a keratinization disorder with an inflammatory and/or immunoallergic component and, in particular, all forms of psoriasis, whether it is

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cutaneous, mucous or unguial psoriasis and even psoriatic rheumatism, or alternatively cutaneous atopy, such as eczema or respiratory atopy or alternatively gingival hypertrophy; the compounds can also be used in 5 certain inflammatory complaints which have no keratinization disorder; for treating all dermal or epidermal proliferations, whether benign or malignant and whether they are of viral origin or otherwise, such as common warts, flat warts and verruciform 10 epidermodyplasia, oral or florid papillomatoses and proliferations which may be induced by ultraviolet radiation, in particular in the case of basocellular and spinocellular epithelioma; for treating other dermatological disorders such as bullosis and collagen 15 diseases; for treating certain ophthalmological disorders, in particular corneopathies; for repairing or combating ageing of the skin, whether this is light-induced or chronological ageing, or for reducing actinic keratoses and pigmentations, or any pathologies 20 associated with chronological or actinic ageing; for preventing or curing the stigmata of epidermal and/or dermal atrophy induced by local or systemic corticosteroids, or any other form of cutaneous atrophy; for preventing or treating cicatrization 25 disorders or for preventing or repairing stretchmarks, or alternatively for promoting cicatrization; for combating disorders of sebaceous functioning such as the hyperseborrhoea of acne or simple seborrhoea; in

the treatment or prevention of cancerous or precancerous states, more particularly promyelocyte leukaemias; in the treatment of inflammatory complaints such as arthritis; in the treatment of any general or 5 skin complaint of viral origin; in the prevention or treatment of alopecia; in the treatment of dermatological complaints having an immunological component; in the treatment of complaints of the cardiovascular system such as arteriosclerosis, 10 hypertension, non-insulin-dependent diabetes and obesity; in the treatment of skin disorders due to an exposure to U.V. radiation.

16. Pharmaceutical composition, characterized in that it comprises, in a 15 pharmaceutically acceptable support, at least one of the compounds as defined in any one of Claims 1 to 13.

17. Composition according to Claim 16, characterized in that the concentration of compound(s) according to one of Claims 1 to 13 is between 0.001% 20 and 5% by weight relative to the composition as a whole.

18. Cosmetic composition, characterized in that it comprises, in a cosmetically acceptable support, at least one of the compounds as defined in 25 any one of Claims 1 to 13.

19. Composition according to Claim 18, characterized in that the concentration of compound(s) according to one of Claims 1 to 13 is between 0.001%

and 3% by weight relative to the composition as a whole.

20. Use of a cosmetic composition as defined in either of Claims 18 and 19, for body or hair  
5 hygiene.

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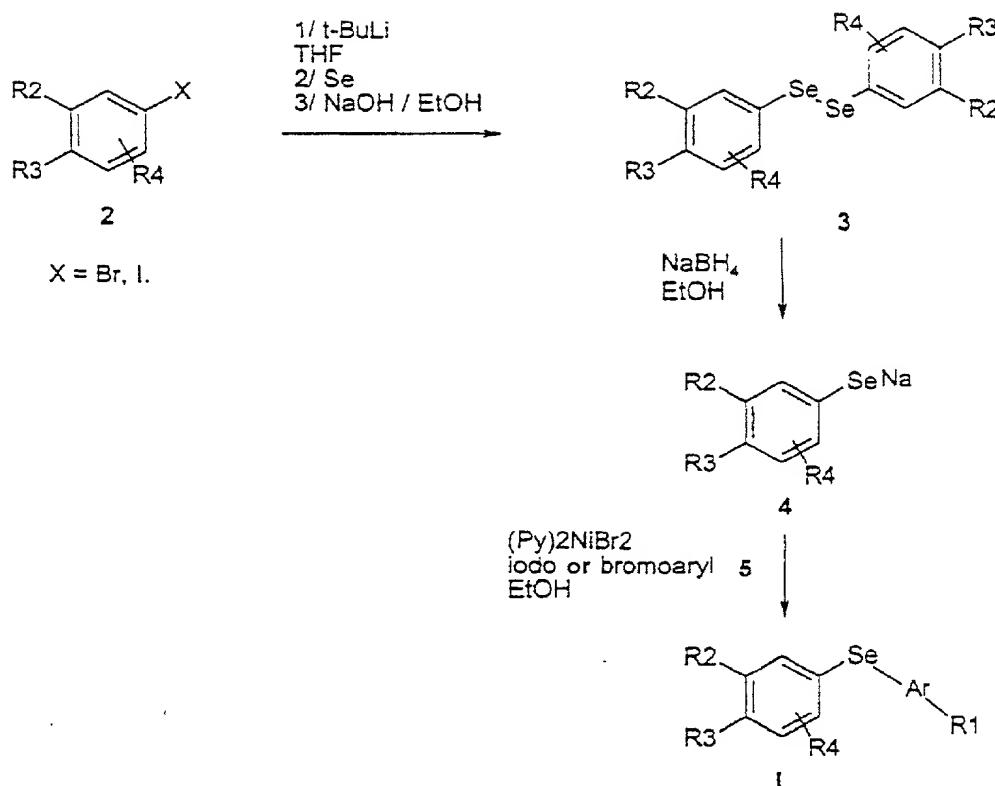


FIGURE 1

**COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY**  
 (Includes Reference to Provisional and PCT International Applications)

Attorney's Docket No.  
 016800-425

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name;  
 I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

**DIARYSELENIDE COMPOUNDS AND THEIR USE IN HUMAN OR VETERINARY MEDICINE**  
**AND IN COSMETICS**

the specification of which (check only one item below):

is attached hereto.  
 was filed as United States application

Number \_\_\_\_\_  
 on \_\_\_\_\_  
 and was amended  
 on \_\_\_\_\_ (if applicable).

was filed as PCT international application

Number PCT/FR99/01389  
 on 11 June 1999  
 and was amended  
 on \_\_\_\_\_ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(e) of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

**PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. §119:**

COUNTRY (if PCT, indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 U.S.C. §119
FR	98/07439	12 June 1998	<u>X</u> Yes <u>  </u> No
			<u>  </u> Yes <u>  </u> No
			<u>  </u> Yes <u>  </u> No
			<u>  </u> Yes <u>  </u> No
			<u>  </u> Yes <u>  </u> No

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below.

\_\_\_\_\_ (Application Number)

\_\_\_\_\_ (Filing Date)

\_\_\_\_\_ (Application Number)

\_\_\_\_\_ (Filing Date)

**COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (CONT'D)**  
 (Includes Reference to Provisional and PCT International Applications)

Attorney's Docket No.  
 016800-425

I hereby claim the benefit under Title 35, United States Code, §120 of any United States applications(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose to the Office all information known to me to be material to the patentability as defined in Title 37, Code of Federal Regulations §1.56, which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

**PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. §120:**

U.S. APPLICATIONS		STATUS (check one)		
U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED
PCT APPLICATIONS DESIGNATING THE U.S.				
PCT APPLICATION NO.	PCT FILING DATE	U.S. APPLICATION NUMBERS ASSIGNED (if any)		

I hereby appoint the following attorneys and agent(s) to prosecute said application and to transact all business in the Patent and Trademark Office connected therewith and to file, prosecute and to transact all business in connection with international applications directed to said invention:

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**21839**

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**21839**

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signature

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RESIDENCE		CITIZENSHIP	
POST OFFICE ADDRESS			
FULL NAME OF FIFTH JOINT INVENTOR, IF ANY		SIGNATURE	DATE
RESIDENCE		CITIZENSHIP	
POST OFFICE ADDRESS			
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RESIDENCE		CITIZENSHIP	
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POST OFFICE ADDRESS			